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SSC Session – Biorheology at ISTH 2023 Congress
06/25/23 16:30-18:30 ET
Room 511

Chair and Co-chairs:
David Bark, Chair
Abhishek Jain, Co-chair
Lining (Arnold) Ju, Co-chair
Karin Leiderman, Co-chair
Paola van der Meijden, Co-chair
Cecile Oury, Co-chair
Anna Waterhouse, Co-chair

Meeting Minutes
I. David Bark: Introduction and Agenda Review

II. Speaker Presentation Notes

A. Karin Leiderman: Mathematical models of coagulation as hypothesis generating tools
Mathematical models can offer insight and efficiency in studying coagulation, but these models come in different types to address different questions. Multiple hypothesis-generating example models are presented. From early basic models of thrombin generation to later models involving protein ensembles varied within physiological ranges, it becomes possible to explain variability in thrombin generation. Recent models provide an explanation for the phenotypic variability in hemophilia A, with a hypothesis tested through experiments. This was accomplished by inputting random combinations of clotting factors into a model to determine which combination most enhanced thrombin generation. This was further extended to include TFPI and AT inhibition. Final thoughts were that models come in many different forms with results that depend on the model; models can be used as hypothesis generating tools, minimizing the number of experiments that may need to be conducted; and iterations between mathematical models and experiments can be more beneficial than either approach isolated on its own. A thrombin generation
simulator is available at http://clotsims.app based on the work discussed by this presenter.

B. Debanjan Mukherjee: Computational model of primary thrombosis

Perspectives were provided on key aspects underlying computational modeling innovations in thrombosis. Types of analysis and investigations based on computational models of thrombosis were discussed based on what they enable us to do; and what kinds of information are generated by state-of-the-art models. The speaker illustrated these aspects using examples from their own research in flow-mediated transport in arterial thrombus neighborhoods. Then they emphasized the importance and value of data integration for in silico models, demonstrating examples from their research on integrating in vivo intravital data with in silico modeling. The talk was closed with some additional perspectives on the importance of validation, identifying key questions such as questions related to hemorheology and clot mechanics/rheology in thrombosis, and the benefits originating from leveraging open-source technologies for modeling.

C. Cecile Oury: Developing new materials for blood-contacting medical devices

Blood-contacting medical devices are prevalently used, but are risk for thrombosis and bacterial infection. The focus, here, is on reducing these complications for prosthetic heart valves by developing new materials. Mechanical heart valves are durable, but lead to thrombosis, while bioprosthetic valves are hemocompatible, but not very durable. Similarly infection is a concern for prosthetic valves, like most blood-contacting devices. The current work focuses on a coating that can be both antimicrobial and antithrombotic through a multilayer cross-linked nanoreservoir with a drug release consisting of Ticagrelor and minocycline. With the coating, it’s possible to greatly release the surface coverage of platelets, as well as the aggregate size on a coated surface. This coating was also found to be durable, did not greatly impact the effective orifice area, or regurgitation of a mechanical heart valve. With an in-house thrombotic tester of heart valves, it was also shown that coated valves were very resistant to thrombosis. Through an in vivo pig model, it was found that the coating had an antithrombotic effect, when compared with the native materials of the valve. A company was generated around this coating and catheters have begun to be investigated. In addition to coating, new bulk materials are being created, with a specific focus on polymeric valve using non-isocyanate polyurethane.

III. Q&A

IV. Speaker Presentation Notes
A. Yunfeng Chen: Differential modulation of platelet adhesion and aggregation by von Willebrand factor as a new strategy to inhibit arterial thrombosis

Arterial thrombosis is a highly lethal disease that lacks efficient cure. Platelets bind to surface immobilized von Willebrand factor (VWF) for adhesion, but also interact with soluble VWF to achieve aggregation. How different VWF functions respectively regulate hemostasis and thrombosis remain unclear. Guided by biophysical principles, the speaker and colleagues created a mutation R636/K642/643A in VWF A1 domain named M13, which was able to weaken shear-induced platelet aggregation, but still supports single platelet adhesion under varied shear rates. An VWF antibody named NMC4 has similar effects in differentially modulating platelet aggregation and adhesion. Importantly, by testing NMC4 in mice expressing human GPIbα and human VWFA1, they showed that NMC4 could prevent occlusive arterial thrombosis without causing excessive bleeding under a certain dose range. Results indicated that platelet aggregation and platelet adhesion are respectively more important to arterial thrombosis and hemostasis. Therefore, selectively inhibiting platelet aggregation may prevent arterial occlusion without compromising hemostasis.

B. Niklas Boknas: Inhibiting the mechano sensing during in vivo thrombus formation

The focus of this talk is on developing a high-resolution technique in both time and space, combined with an approach to investigate thrombus contractile characteristics. Through the technique of labeling a subset of a platelets, it’s possible to track platelets at scales from a global level to a individual cell level, with different levels of stress throughout the scales. The method developed involves a repeatable scanning-laser-induced endothelial injury. Deep learning segmentation was performed with Python. A coordinate system is created along the flow direction, while platelets are tracked. Many different variables are tracked, giving a tremendous amount of data. In this work, investigators looked at inhibition of PI3 kinase C2a. Inhibition leads to a smaller thrombus structure after 2 minutes compared to controls based on platelet counts. Larger thrombi which much more greatly effected when compared to smaller thrombi. It specifically appears to be the outside of the thrombi that is most impacted. Other inhibitors affect all thrombus sizes and time of growth.

V. Q&A

VI. David Bark, Abhishek Jain, and Karin Leiderman: Discussion on Biorheology SSC Direction
A two way discussion was had with the audience. One area for the future is to look at different scales, e.g. sex differences or population differences from the protein level up to overall thrombotic growth. A second comment suggested that the SSC look at benchmarks for verification and validation of computational models. In addition, it would be beneficial to compile a publication involving common inputs to models. One more suggestion is to summarize what is known about shear-induced platelet activation. A final comment was how the audience enjoyed the combined efforts of clinicians and engineers in the session.

VII. **David Bark: Session Wrap-up**
Meeting Minutes

I. Call to Order

II. Agenda Review

III. Speaker Presentation Notes

A. Extended secondary prevention of recurrent thrombotic events with low-dose direct oral anticoagulants in patients with splanchnic vein thrombosis (Walter Ageno). The study aims to assess the safety and efficacy of low dose DOACs for the extended secondary prevention of venous and arterial thrombosis in 250 patients with splanchnic vein thrombosis. Patients who have safely completed at least 3 months of full dose anticoagulant treatment will be eligible. Treatment duration will be 12 months. Several European and North American centers are expected to participate. This project has just received a large SSC ISTH grant award.

B. International registry on the use of the direct oral anticoagulants for the treatment of unusual site VTE (Walter Ageno). This study was promoted through the SSC Control of Anticoagulation and was started in 2018. Recruitment will be completed at the end of 2023. The registry aims to assess the safety and effectiveness of the DOACs in patients with unusual site venous thrombosis and also the rationale for their use in clinical practice. A minimum follow-up of 6 months and a maximum of 12 months is requested. As of June 19th 2023, 255 patients have been enrolled in 20 countries from the USA, Europe, and Thailand. About 60% of patients have splanchnic vein thrombosis and 30% have cerebral
vein thrombosis. However, the DOACs have also been prescribed to patients with other unusual sites including ovarian, renal, and retinal vein thrombosis.

C. **Surveys on antithrombotic therapy in patients with cancer** (Deborah Siegal). We are conducting an anonymous international online survey of healthcare providers who manage antithrombotic therapy in patients with cancer who experience ischemic stroke. This is a joint project of the SSC on Control of Anticoagulation and SSC on Hemostasis and Malignancy. The overall goal of the survey is to assess physician preferences regarding the management of cryptogenic stroke in patients with active cancer in the following domains: (i) acute reperfusion therapies (intravenous systemic thrombolysis, mechanical thrombectomy, and (ii) antithrombotic therapies for secondary prevention (anticoagulants, antiplatelet therapy). The primary objective is to understand physician preferences regarding acute stroke treatments (systemic thrombolysis, mechanical thrombectomy) and antithrombotic therapy (antiplatelet and/or anticoagulant) in patients with active cancer. The main secondary objective is to explore potential differences in treatment based on respondent and cancer characteristics, variability in management by subgroups, and areas of further study interest. To date, 53 respondents from a variety of countries and specialties have completed the survey. We solicited additional input from SSC members and their colleagues with a goal of more than 100 respondents.

D. **Reducing hospital-acquired venous thromboembolism in specialized hospitals through pharmacist-led collaborative team approach** (Tamrat Assefa). First, I would like to thank ISTH SSC Anticoagulation Control for giving me an opportunity to on a research project entitled Reducing Hospital-Acquired Venous Thromboembolism in Ethiopian Specialized Hospitals through Pharmacist-Led Collaborative Team Approach: (RHA-VTE) Project. The purpose of the proposed research with its specific objectives and how it will be implemented was presented. The project timeline and required budget way forward in finding collaborators and submitting the full proposal for funding were also addressed during the presentation. Feedback was given to some questions and comments raised by the audience. Finally, some scholars recommended approaching/implementing the project by establishing Anticoagulation Stewardship Program and this was carefully noted in future work of the project.

E. **Clinical value of the thrombin generation assay as a tool to monitor anticoagulation reversal** (Herm-Jan Brinkman). Herm-Jan Brinkman discussed
the usefulness and limitations of the thrombin generation assay (TGA) as a tool to study reversal of oral anticoagulation and to guide management of severe bleeding. The TGA is potentially a very useful test to monitor reversal of anticoagulation by vitamin K antagonists as well as direct oral anticoagulants. There are however several issues related to standardization and validation and consensus on TGA outcome and correction of hemostasis is lacking. Clear guidelines on how to perform a TGA in case of anticoagulation reversal is of utmost importance.

**F. Optimizing HIT diagnosis: The need for optimizing confirmatory tests** (Noppacharn Uaprasert). Heparin-induced thrombocytopenia (HIT) confirmation requires functional assays to detect heparin-dependent platelet-activating antibodies. These tests are crucial for avoiding the overdiagnosis and overtreatment of HIT, as well as preventing unnecessary avoidance of heparin use. Despite the availability of several HIT confirmatory tests, they come with various limitations and challenges. For instance, the serotonin-release assay (SRA) and heparin-induced platelet activation (HIPA) are technically complex and can only be performed in specialized reference centers. Flow cytometry-based assays still lack standardization and validation, leading to variable sensitivity and specificity across different laboratory centers. Furthermore, platelet aggregometry testing has limited sensitivity for confirming HIT. Therefore, it is imperative to enhance the ease and sensitivity of confirmatory assays through robust standardization and validation. By doing so, these tests can be widely adopted by most platelet laboratory centers, ultimately improving the diagnosis of HIT on a global scale.

**G. Monitoring of LMWH in renal dysfunction (Karina Meijer).** This working group seeks to find evidence for rational dosing of low molecular heparin in patients with renal dysfunction. Progress reported included the results of a questionnaire, which mainly showed considerable variation in clinical practice. Second, results of a study on nadroparin dosing showed that aXa measurements were disappointing. They varied widely between labs, and achieved levels were generally low, both in patients with, and those without renal dysfunction. Plans presented were a systematic review of available literature. Also, the working groups seeks collaboration with colleagues who have access to aXa measurements in cohorts on enoxaparin.
H. Persistent and annoying issues related to laboratory monitoring of unfractionated heparin: Which test? Which reagent? Which target? (Isabelle Gouin-Thibault). Despite decades of use of UnFractionated Heparin, there remain many unresolved questions concerning its the management, which lead to a wide heterogeneity of the practices: the determination of the therapeutic ranges, the minimal antithrombin plasma level required for effective anticoagulation, the so-called "heparin resistance", the place for aPTT in the monitoring, the limitations of anti-Xa assays that lack harmonization with the issue of whether to add dextran. In order to improve management, additional clinical data in currently treated patients are needed, as well as guidance on the management including nomogram, test, reagents... We propose to develop a survey on the UFH management to first get information on the practices.

I. Updated guidance for efficacy and safety outcomes for pediatric venous thromboembolism clinical trials (Hilary Whitworth). The Control of Anticoagulation SSC collaborated with the Pediatric SSC to update the recommended outcome definitions for pediatric venous thromboembolism clinical trials. A task force of members from both SSCs reviewed the original 2011 guidance statement, recent pediatric clinical trials, recommended outcome definitions in adults, and regulatory guidance and came to consensus to provide this update. This included a new bleeding category called "Patient Important Bleeding, No Intervention" which captures bleeding for which someone seeks medical care, but no changes are made to the medical plan. They also clarified the definitions of clinically relevant non-major bleeding, included menstrual bleeding in any category for which the criteria are met, and removed asymptomatic recurrent VTE and VTE-related mortality from the recommended primary efficacy outcome.

J. Recommendations on nomenclature for emerging anticoagulant medications (Geoffrey Barnes). As newer anticoagulants targeting factors XI/XIa and XII/XIIa are under development, there is a need to agree on a nomenclature scheme that will harmonize communication among clinicians and researchers globally. An expert panel was assembled to develop draft recommendations and public comment was obtained from the global thrombosis and hemostasis community. The panel recommends that all anticoagulants are referred to by both their specific target and mode of administration (e.g., oral factor XIa inhibitor, parenteral factor XII inhibitor) to avoid confusion and broad generalization that may apply all anticoagulant medications.
IV. **Conclusion/Any additional notes**
At the end of the meeting, Dr. Cuker acknowledged his co-chairs and welcomes Dr. Lana Castellucci as the new Chair. He also thanked the audience for attending and welcomed them to become active in the SSC by submitting projects or ideas for communications and guidance.
SSC Session - Disseminated Intravascular Coagulation
24th June 2023 14:30 – 16:30 ET
Room 511

Attendees:
Ecaterina Scarlatescu, Chair DIC SSC/Moderator, Speaker
Maha Othman, Co-Chair DIC SSC/Moderator
Offer Erez, Co-Chair SSC Subcommittee on Women’s Health Issues in Thrombosis and Hemostasis /Speaker
Hunter Moore, Co-Chair DIC SSC /Speaker
Toshiaki Iba, Past Chair DIC SSC/ Speaker
Yutaka Umemura, ISTH member/ Speaker

Meeting Minutes

I. Call to Order
The session started with a presentation of the Co-Chairs, and of the ongoing projects of the DIC SSC. Possible collaborators were invited to visit the web page of the DIC SSC, to fill the Expression of Interest Form, and to apply for the Co-Chair position for the upcoming years.

II. Agenda Review
The topics and speakers of the DIC SSC Session were briefly revised, and the participants were invited to prepare questions for the Q&A sessions in the middle and at the end of the program.

III. Speaker Presentation Notes

A. Speaker 1: Nathan Nielsen Title: Updates in the DIC registry project- virtual presentation (recorded)
An update of the DIC registry was presented. The DIC registry includes ICU patients who have a risk factor for DIC from 8 centers in Europe and the US. The Registry aims are to assess the diagnostic and therapeutic approaches of overt DIC, the risk factors for overt DIC, the bleeding or thrombotic events associated with DIC and to identify DIC sub-categories. The preliminary results confirmed sepsis as the most common cause for DIC, and identified a higher incidence of
macrovascular venous and arterial thrombotic events in DIC patients compared to patients without DIC. Several types of bleeding were recorded, with gastro-intestinal bleeding as the most frequent cause of bleeding. Almost half of the DIC patients presented with both bleeding and thrombotic complications. The identified risk factors were: for thrombosis- renal replacement therapy, for bleeding- the vasopressor support and for both bleeding and thrombotic event the
identified risk factor was mechanical ventilation.

B. Speaker 2: Ecaterina Scarlatescu Title: New Registry on DIC in liver cirrhosis
An accurate diagnosis of DIC in cirrhotic patients is difficult, due to the overlap of hemostatic profiles in DIC and cirrhosis, possibly leading to DIC over-diagnosis in particular in patients with advanced stages of liver disease. The Subcommittees of DIC and Hemostatic Management of Patients with Liver Disease started in 2023 a prospective registry for assessing the current DIC diagnostic and therapeutic approaches in cirrhotic patients. Findings from this project will offer a better image of DIC diagnosis and management in patients with chronic liver disease by analyzing a large database of patients with different stages of liver disease and their hemostatic tests obtained in regular clinical practice and will represent a step forward in the development of a specific DIC score for cirrhosis patients.

C. Speaker 3: Offer Erez Title: Registry on DIC in Pregnancy- Final Update and Lessons Learned
DIC affects about 0.03% of pregnant women in developed countries and can reach up to 1% in low and middle outcome nations. We established an international registry on DIC in pregnancy to better understand the characteristics of this life-threatening complication. Overall we had 145 entries; of them, 104 inserted also clinical data and 81 patients had a complete dataset. Most of the hospital participating had between 2000-5000 deliveries a year and treated between 1-10 DIC cases annually. The majority of women were diagnosed postpartum with overt bleeding. The most prominent antepartum complication was placental abruption and uterine atony was the prominent feature post-partum. The different DIC scores varied substantially in the diagnosis of DIC, and the pregnancy specific DIC had the highest rate of agreement with clinical definition of DIC. DIC carries substantial maternal morbidity including hysterectomy renal and respiratory failure and maternal death.

D. Speaker 4: Yutaka Umemura Title: A Machine Learning Model for Early and Accurate Prediction of overt-DIC before its progression to an overt stage
Prediction of patients likely to progress overt-DIC before its progression to overt stage is important to use anticoagulants for appropriate patient at the earlier timing. In this retrospective observational study including 912 adult septic patients, we aimed to develop an early prediction model for overt-DIC using machine learning technology. Among the study patients, approximately
15% of the septic patients without DIC later developed overt-DIC within 7 days from admission. A machine learning model constructed using LightGBM method, could predict the progression of overt-DIC with higher accuracy compared to conventional early diagnostic criteria. Circulation parameters, such as urine output and lactate, were repeatedly used in the model, suggesting that these parameters were strongly associated with the later progression of overt-DIC.

E. Speaker 5: Toshiaki Iba Title: Sepsis-induced coagulopathy and DIC

In response to the growing interest in early intervention with anticoagulant therapy for DIC, the ISTH DIC/SSC introduced sepsis-induced coagulopathy (SIC) as a practical diagnostic criterion in 2019. SIC is designed specifically for diagnosing DIC in sepsis, and it allows scoring based on two coagulation markers, platelet count and prothrombin time (PT-INR). Several years have passed since its introduction, and the diagnostic characteristics of SIC are being reported. Firstly, the incidence rate of SIC is around 20% in patients with sepsis, and approximately twice the rate of overt DIC. The mortality rate has been reported to be around 30%, indicating the need for intervention. Retrospective studies have shown the effectiveness of anticoagulant therapy using heparin, antithrombin, and thrombomodulin. The simplicity of SIC allows for repeated evaluations, making it potentially applicable in routine clinical practice.

F. Speaker 6: Hunter Moore Title: Strengths and weaknesses of identification of DIC with viscoelastic testing

Disseminated intravascular coagulation (DIC) is a lethal pathophysiology caused by systemic activation of coagulation causing resulting in consumptive coagulopathy and derangements in fibrinolysis. DIC treatment is addressing the underlying cause while transfusing hemostatic blood products to correct life threatening coagulopathy. Emerging data supports anticoagulation strategies may have therapeutic benefit. However, off target therapeutics can cause iatrogenic bleeding and death as appreciated in prior clinical trials. Viscoelastic testing (VET) has emerged as a promising tool to identify early DIC, as there appears to be a precursor hypercoagulable state regardless of underlying cause. Conventional clinical assays with VET hold potential for early DIC identification and treatment, but certain limitations exist. This talk reviews the evolving concepts of VET in identification of patients with DIC to highlight future opportunities for clinical implementation to improve outcomes in patients with this highly lethal disease process.

IV. Conclusion/Any additional notes

The session provided enough time for the Q&A, and attendees had the opportunity to ask questions in the 2 question breaks in the middle and at the end of the session. With the exception of the first speaker who was unable to attend the meeting and provided the recorded lecture, all the other speakers answered the questions from the audience.
Meeting Minutes

I. Call to Order: Dr Escobar welcomed everyone to the meeting and provided a brief introduction and overview about the program

II. Agenda Review: Dr Escobar presented the agenda for the meeting

III. Speaker Presentation Notes

A. Speaker: Stacey Croteau

Endpoints and outcomes with new therapies in hemophilia A and B

Discussed emergent biologics in hemophilia and recently approved hemophilia therapies; endpoints and outcomes utilizing factor concentrates in hemophilia A and B; endpoints and outcomes in gene therapy in hemophilia A and B; AAV-mediated gene transfer effectiveness and safety and endpoint and outcomes of substitution therapies and rebalancing therapies. Concluded: 1. The expanding portfolio of hemophilia therapy options allows for an increasingly individualized approach to care; 2. Gene and cellular therapies provide a promising approach to improving or normalizing FVIII, FIX, and other coagulation protein levels and reducing the burden of therapy; 3. Ongoing assessment of short-term and longer term expression reliability, variability, durability, and safety of these approaches are needed; 4. Rebalancing therapies may provide additional prophylaxis options particularly for those sub-populations not adequately managed on currently available therapies; 5. Risk of thrombosis and increased complexity of hemostatic management in the setting of comorbidities, major bleed/injury or critical illness require thoughtful
The need for patient engagement in understanding options, verbalizing goals, and collaborative provider-patient decision making is more important than ever.

B. Speaker: Dr Roberta Gualtierotti

**Is it time to standardize MSK ultrasound in hemophilia?**

The advent of novel effective treatment and the identification of the need to achieve a higher trough level for patients with hemophilia has allowed a shift of the treatment target in hemophilia from survival and prevention of life-threatening complications to prevention of musculoskeletal complications and improvement of quality of life.

Point-of-care musculoskeletal ultrasound imaging has also improved the early recognition of joint bleeding and the differential diagnosis of acute joint pain. In addition, joint ultrasound allows the evaluation of the severity of hemophilic arthropathy in terms of synovitis and osteochondral damage. However, different scoring methods for joint damage are currently available for ultrasound imaging and a shared definition of the ultrasound characteristics of joint bleeding is currently lacking. A lack of standardisation may lead to an incorrect evaluation of the presence and progression of joint damage in hemophilia.

We propose to start a standardisation process for definitions of joint complications associated with hemophilia to identify early joint damage and prompt a personalised management. We advocate this process to be part of the Factor VIII, Factor IX and Rare Coagulation Disorders Subcommittee of the International Society on Thrombosis and Hemostasis Scientific and Standardization Committee (SSC program).

C. Speaker: Roger Schutgens

**Anticoagulation and anti-platelet agent in hemophilia**

Cardiovascular disease is an emerging medical issue in patients with hemophilia (PWH) and its prevalence is increasing up to 15% in PWH in the United States. Atrial fibrillation, acute and chronic coronary syndromes, venous thromboembolism, and cerebral thrombosis are frequent thrombotic or prothrombotic situations, which require a careful approach to fine-tune the delicate balance between thrombosis and hemostasis in PWH when using both procoagulant and anticoagulant treatments. Generally, PWH could be considered as being naturally anticoagulated when clotting factors are <20 IU/dL, but specific recommendations in patients with very low levels according
to the different clinical situations are lacking and mainly based on the anecdotal series. For PWH with baseline clotting factor levels >20 IU/dL in need for any form of antithrombotic therapy, usually treatment without additional clotting factor prophylaxis could be used, but careful monitoring for bleeding is recommended. For antiplatelet treatment, this threshold could be lower with single-antiplatelet agent, but again factor level should be at least 20 IU/dL for dual antiplatelet treatment. In this complex growing scenario, the European Hematology Association in collaboration with the International Society on Thrombosis and Haemostasis, the European Association for Hemophilia and Allied Disorders, the European Stroke Organization, and a representative of the European Society of Cardiology Working Group on Thrombosis has produced this current guidance document to provide clinical practice recommendations for health care providers who care for PWH.

D. Speaker: Diane Nugent

**FVII deficiency: the discrepancy between levels and phenotype**

Presented data on 674 individuals and 20,720 genes that have been sequenced. Discussed ATHN 10 custom gene panel. Results showed that 30% of individuals had more than 1 variant in the F7 gene and no variants were identified in 5% of individuals. In addition, 38% had a variant in a second gene F7 haplotype (-325,64+9,R413Q) and 42% had a VUS. Variants that affect the serine protease can have normal bleeding scores despite having low FVII levels. It is possible that there are modifying genes and variants in the tissue factor molecule that are unknown and affect the FVII levels. FVII Padua is an example of a variant that can show variability on the assays depending on the type of tissue thromboplastin that is used.

E. Speaker: Helen Wilmot

**Proposal for the replacement of the 6th International Standard for FVIII/VWF, Plasma**

A replacement for the 6th International Standard for FVIII/VWF, Plasma, is required, due to steadily depleting stocks. This presentation described the timelines for the production of the 7th International Standard and the analytes which are to be assigned in International Units. Interested parties able to perform assays for any of the FVIII or VWF analytes were invited to take part in the collaborative study for value assignment of the 7th IS, scheduled for 2024, and can register their interest via email.
F. **Speaker: Sanj Raut**  
**Value Assignment to the WHO 9th International Standard for FVIII Concentrate: update**  
Five candidate materials, 3 plasma-derived (samples A, B and C) and 2 recombinants (samples D and E), have been evaluated as potential replacements for the WHO 8th International Standard (IS) for FVIII concentrate, by assays relative to the current primary WHO 8th IS, in an international collaborative study involving 26 laboratories. Overall, sample A is the favoured candidate for the following reasons: (a) Near complete agreement in mean values obtained by the one-stage and chromogenic methods, whereas all other candidates displayed some discrepancies, being statistically significant for all except for samples B & D, (b) Lowest overall inter-laboratory variability for combined estimates (GCV=2.4%) from both methods. This study confirms that the proposed IS (sample A) will be suitable for measurement of FVIII therapeutic concentrates. The excellent parallelism of assays for both methods, relative to the current WHO 8th IS FVIII concentrate, validates its suitability for measurement of FVIII therapeutic concentrates using both chromogenic and one-stage clotting assays. Following agreements by all study participants, ISTH/SSC Experts, WHO-ISTH Liaison Group and the SSC Board, the study was presented to the WHO/ECBS, Geneva, Switzerland, in March 2023, where the above proposal was accepted and preparation 21/142 was established as the WHO 9th IS Factor VIII Concentrate with an assigned potency of 9.5 IU/ampoule.

G. **Speaker: Samantha Gouw**  
**MAPTO survey presentation summary**  
Since emicizumab became available, children with severe hemophilia may only use factor VIII (FVIII) concentrate occasionally. It is currently unknown whether additional regular administration of FVIII is required to obtain tolerance towards FVIII or whether the effect is the opposite and FVIII exposure rather triggers inhibitor development. In order to gain insights into the current practices and perspectives of hemophilia treaters worldwide on obtaining FVIII tolerance in previously untreated patients (PUPs) with severe hemophilia A who use emicizumab prophylaxis, we are conducting the MAPTO survey. This international online survey will be distributed to all hemophilia treatment centers worldwide and will contain questions on perceived risks associated with inhibitor development, the clinical and psychosocial impact of the prolonged risk period for inhibitor development, the necessity of FVIII tolerization, the willingness to administer intravenous FVIII injections, and the patient types or clinical situations in which FVIII tolerization is deemed appropriate. Our project will potentially reveal domains of heterogeneity in perspectives and clinical
practices of hemophilia treatment worldwide that will guide the design of future research into concomitant FVIII infusions besides emicizumab prophylaxis. This study is conducted by investigators at the Academic Medical Center Amsterdam in close collaboration with an international steering board of hemophilia experts. If you want to participate in the MAPTO study, send an email to MAPTO@amsterdamumc.nl or contact Lilianne van Stam/Samantha Gouw via l.e.vanstam@amsterdamumc.nl

H. Speaker: Guy Young
New Nomenclature for PUPs: update
A schema for a new nomenclature for previously untreated patients which has been worked on for the past 2 years was presented. The nomenclature based on PedNet PUP data provided new groups for pure PUPs (0 exposure days) and for those with up to 7 or 8 exposure days, a second group for those between 8-9 up to 20-21 exposure days and a group with more than 20 exposure days. There was robust discussion as to whether such a new nomenclature schema is even needed and if so if we had the numbers right. Further discussion will be held in the future to address these points.

IV. Conclusion/Any additional notes
Dr Escobar adjourned the meeting
Meeting Minutes

I. Call to Order

Tetsumei Urano, MD, PhD - Shizuoka Graduate University of Public Health

Fibrinolysis is finely regulated by a spatiotemporal mechanism, and its disruption leads to either thrombosis or bleeding. This subcommittee has been focusing on how we can detect such disorders of the regulatory mechanism and how quickly and adequately such disorders could be managed. Today we also focus on the understanding of the pathophysiologic disorders of fibrinolysis and discuss suitable diagnostic tools.

II. Agenda Review

Wide variations in plasma fibrinolytic activities after tPA treatment in real world stroke patients, and the influence of plasminogen levels pyothorax in the pleural cavity on their outcome after tPA treatment, as well as preventive effects of tranexam acid on postoperative recurrence after surgery for chronic subdural hematoma are introduced from the clinical side. Euglobulin clot lysis (ECLT) based diagnostic strategy for bleeding patients, as well as new TAFIa assay are introduced from the basic research field. Current situation of WHO standards of TAFI and PAI-1 is also presented.

III. Speaker Presentation Notes

A. The in vivo response to tPA varies over 100-fold in patients with acute ischaemic stroke...is this predictive of thrombolysis outcome?

Robert Medcalf, PhD – Monash University, Melbourne, Australia.
Thrombolysis using tissue-type plasminogen activator (tPA) for patients with acute ischaemic stroke (AIS) is of no clinical benefit in over 60% of patients. We determined whether changes in the host’s capacity to respond to tPA may play a role. We evaluated changes in baseline levels of plasmin-antiplasmin (PAP) complexes in pre-thrombolysis and 1h post-thrombolysis plasma from 289 patients with AIS. We also quantitated inducible PAP levels in pre-thrombolysis plasma following treatment with tPA in the presence (maximal activation) and absence (systemic activation) of soluble fibrin to determine fibrinolytic capacity. We observed that the response to both tPA and tPA+soluble fibrin varied over 100-fold. Moreover, the lower capacity to respond to tPA systemically compared to its maximal capacity in the presence of fibrin correlated with improved clinical outcome.

B. Plasminogen content in empyema and the role for supplementation in intrapleural lytic therapy.

Chris Barrett, MD – University of North Carolina at Chapel Hill

Inflammatory proteases from neutrophils are known to cleave plasminogen, the zymogen of the terminal fibrinolytic protease plasmin. Patients with pleural space infections are often difficult to treat because fibrin loculations form that prevent adequate drainage of the infection with tube thoracostomy alone. As such, the clinical standard is currently to instill tissue-plasminogen activator (tPA) and DNAse into the pleural space via a thoracostomy tube six times over three days in an attempt to break up the fibrin loculations and drain the infection. While this approach has efficacy in many cases, it can be incomplete and there is also an outright failure rate of approximately 20%. Given that pleural fluid from infected pleural cavities is known to have a high neutrophil content, our group has hypothesized that this inflammatory fluid is unlikely to contain sufficient plasminogen for a robust lytic response to tPA and that plasminogen supplementation would improve the success rates of intrapleural lytic therapy and also reduce the number of doses of tPA and DNAse required to achieve success. If successful, this approach would also be expected to reduce hospital days and need for surgery in patients with pleural space infections.

C. Fibrinolytic assays in the diagnostic work up of patients with an increased bleeding tendency

Saskia E.M. Schols, MD, PhD. Radboud university medical center, The Netherlands
In the Hemophilia Treatment Center Nijmegen-Eindhoven-Maastricht, location Radboudumc, we perform a stepwise diagnostic procedure for patients with an increased bleeding tendency. During the first and second steps, screening hemostatic assays are performed. However, if there is no established diagnosis after the second step, fibrinolytic assays are undertaken, consisting of PAI-1 antigen and activity level, α2-antiplasmin level and the euglobulin clot lysis assay before and after venous compression (ECLT ratio before/after). A retrospective cohort study in our HTC revealed that there was a significant number of patients with a presumptive fibrinolytic disorder (PAI-1 deficiency or increased ECLT ratio) of nearly 40% compared to the total group of patients in whom fibrinolytic assays were performed. In addition, patients with a presumptive fibrinolytic disorder were more likely to have an increased ISTH BAT score of >10 as an indication for the fibrinolytic analysis.

D. Preventative effect of TXA on postoperative recurrence after Burr hole surgery for chronic subdural hematoma

Akinori Miyakoshi, MD, PhD, MPH – Shizuoka Graduate University of Public Health, Dept. of Neurosurgery, Shizuoka General Hospital, Japan

This retrospective study aimed to investigate whether oral administration of tranexamic acid (TXA) reduce the occurrence of repeat surgery after burr hole craniotomy (BC) for chronic subdural hematoma (CSDH). A large Japanese local population-based longitudinal cohort in the Shizuoka Kokuho Database between April 2012 and September 2020. Patients included were aged 60 or older and had undergone BC for CSDH. Covariates were collected from records of the preceding 12 months from the month of first BC, and patients were followed up for 6 months after surgery.

Of the 8,544 patients who underwent BC for CSDH, 6,647 were included. After 1:1 propensity score matching, administration of TXA, compared to control, was significantly associated with a lower incidence of repeat surgery (RR 0.38, 95%CI 0.26-0.56). No significant difference was observed for death or the onset of thrombosis. Oral administration of TXA reduced the occurrence of repeat surgery after BC for CSDH.

E. A novel fluorescence-based TAFIa substrate

Michael B. Boffa, PhD – University of Western Ontario, Canada

A first-ever fluorogenic substrate for TAFIa was described, consisting of a Gly-Ala-Gly-Arg peptide modified at its amino terminus with TAMRA, with Evans Blue or Ponceau S as anionic quenchers binding to the cationic side chain of Arg. Removal of Arg by TAFIa results in dissociation of the quencher and hence increased TAMRA
fluorescence. The assay is highly sensitive with a lower detection limit of ~100 pM TAFIa and is linear up to 25 nM TAFIa. Plasma interferes with the assay, stymying the initial goal of real-time monitoring of TAFIa generation during clotting and lysis. However, the assay remains active if the plasma concentration in the assay is limited to 2% and Ponceau S is the quencher, allowing estimation of total TAFI in a plasma sample after treatment with thrombin-thrombomodulin. Immuno-capture implementations are also possible and will be pursued to measure TAFIa in plasma and functional concentrations of soluble thrombomodulin.

F.  Update on WHO IS Projects

Craig Thelwell, PhD – NIBSC, UK

The study to calibrate the proposed WHO 1st International Standard (IS) for TAFI, Plasma is now complete. It is proposed that the candidate material, a normal pooled plasma lyophilised and sealed into glass ampoules and coded 17/200, is established as the 1st IS for TAFI plasma with a value assigned for TAFI activity of 0.87 IU and for TAFI antigen of 0.92 IU per ampoule relative to local plasma pools. It is also proposed to assign a value for TAFI antigen of 7.43 (7.05 – 7.82) µg per ampoule, based on Isotope Dilution Mass Spectrometry (IDMS) analysis. The proposed values were approved by the study participants and the next step is to seek approval from the SSC Subcommittee experts before submitting to the WHO ECBS for establishment in October 2023.

The project leaders for the replacement WHO IS for PAI-1 activity, Plasma and the D-Dimer WHO IS have left the agency. A plan was presented to progress the PAI-1 project through additional testing of the trial fill samples. Attempts to standardise D-Dimer have proved very difficult with stability issues with patient D-Dimer rich plasma and FDP preparations. A patient plasma stabilised with trehalose presents a possible solution but would require support from the subcommittee in sourcing material and with testing trial fill samples.

IV.  Conclusion/Any additional notes

Ernest E Moore, MD – University of Colorado, USA

We had the pleasure of hearing cutting-edge science in clinically relevant studies this afternoon. But it is important to recognize that these insightful studies have been conducted in plasma devoid of platelets, red cells, neutrophils, and macrophages that all contribute to clot structure, a critical component of fibrinolysis regulation. Perhaps we should develop microfluidics systems coated with additional fibrin to enhance the fibrinolytic response to whole blood examined under varying flow conditions.
**Meeting Minutes**

I. **Call to Order: 16:30**

II. **Agenda Review:**
A number of last-minute amendments to the Agenda/Program were needed due to a number of Speakers that were unable to attend (due to personal / family reasons). The changes are highlighted below:
Factor XIII and Fibrinogen SSC Subcommittee Meeting, Room:710B, Montréal, Canada  
Tuesday, June 27 2023, 16:30-18:30 ET (SSC 22.0) PROGRAM

Chair: Sanj Raut (UK)  
Co-Chairs: Zsuzsa Bagoly (HU), Stephen Baker (USA), Akbar Dorgalaleh (IR), Cédric Duval (FR/UK), Marlien Pieters (ZA) and Verena Schroeder (CH)

Introduction
16:30-16:40 Sanj Raut, (NIBSC-MHRA, Potters Bar, UK): Session Welcome & Overview of Subcommittee’s Activities

Standardisation Topics
(Moderators: Sanj Raut, UK; Marlien Pieters, ZA - Each presentation followed by 5 min Questions)
16:40-16:50 Martin Guthold (Wake Forest University, NC, USA):  
Marlien Pieters (North West University, ZA): Update on proposed standardised method for SEM image analysis of fibrin clots - SSC Collaborative Study Project.

Scientific & Clinical Topics
(Moderators: Sanj Raut, UK; Verena Schroeder, CH - Each presentation followed by 5 min Questions)
17:05-17:15 Akbar Dorgalaleh, (Iran University of Medical Sciences, Tehran, Iran): Proposed SSC communication: guidelines for the management of acquired and congenital factor XIII deficiency.
17:05-17:10 Munira Borhany (National Institute of Blood Disease & BMT, Karachi, Pakistan): Comprehensive evaluation of coagulation and fibrinolysis parameters in patients with congenital factor XIII deficiency in Pakistan: Verbal Update from the SSC Project.
17:10-17:15 Sanj Raut, (NIBSC-MHRA, Potters Bar, UK): SSC Strategic Planning and Board Meeting Feedback for Subcommittees
17:35-17:45 Zsuzsa Bagoly, (University of Debrecen, Debrecen, HU): Inactivation of Factor XIII.
17:50-18:00 Stephen Baker, (Wake Forest University, NC, USA): Thrombin concentration has a more prominent effect on fibrin clot density and porosity than fibrinogen concentration alone.

Concluding Remarks & Closing of Meeting:
18:20-18:30 Sanj Raut, (NIBSC-MHRA, Potters Bar, UK)
III. Speaker Presentation Notes

A. Speaker 1:

**Marlien Pieters (North West University, ZA):**

*Update on proposed standardised method for SEM image analysis of fibrin clots - SSC Collaborative Study Project.*

**Background:** In the absence of an internationally accepted standardized method for determining fibrin fiber diameter from scanning electron microscopy (SEM) analysis, a large discrepancy in fiber diameter has been reported in the literature for healthy individuals. This precludes inter-laboratory comparison and prevents the establishment of normal and disease ranges, as are available for other CVD risk factors. **Aim:** To develop a standardized protocol for determining fibrin fiber diameters from SEM analysis of plasma clots. **Methods:** We performed an extensive review of published protocols and synthesized a best practices protocol. This protocol describes, in detail, the steps for clot formation, washing, fixation, dehydration, drying (using both critical point and chemical drying), sputter coating and imaging. The protocol aims to preserve clot structure, and to maintain ionic strength and molality of blood through the fixation step. The protocol also aims to use materials that are widely available and has been tested by nine labs in six different countries. Human α-thrombin and fresh-frozen commercial pooled citrated plasma were provided to the participating labs. **Results:** Labs used the standardized protocol and their respective in-house protocols to prepare and process clots and determine fiber diameter values. These values will be compared and reported, as well as values obtained by centrally analyzing the diameter values using both manual measurement and an automated measurement tool (Diameter J, an Image J plug-in). **Conclusions:** The proposed standardized protocol should aid in diminishing discrepancies in fibrin fiber diameter determination via SEM analysis. This will facilitate interpretation of results, allow direct comparison of data between laboratories and aid in the development of ranges for healthy, prothrombotic and hemophilic individuals.

B. Speaker 2

**Sanj Raut (NIBSC-MHRA, UK):**

*Establishment of and value assignment to the WHO 2nd International Standard for Factor XIII Plasma, (20/292) [WHO replacement standard].*

An international collaborative study, involving 13 laboratories, was carried out to calibrate the proposed World Health Organization (WHO) 2nd International Standard (IS) for Factor XIII (FXIII) plasma for activity, A2B2 antigen and Total FXIII-B subunit levels. This study also investigated the relationships between measurements of FXIII in concentrates vs plasma standard. Potency estimates for the proposed candidate FXIII plasma standard (20/292; coded duplicate samples B and C) and the FXIII
concentrate preparation (D), were all calculated relative to the WHO 2nd IS for FXIII plasma (A). Estimates of FXIII activity for the candidate plasma standard (20/292) showed good agreement between laboratories with a combined inter-laboratory geometric coefficient of variation (GCV) of 3.6% and a combined geometric mean FXIII potency value of 1.04 IU/ml. Assays of the concentrate preparation D relative to 1st IS FXIII showed a relatively good agreement between laboratories with GCV of 8.7% (and a geometric mean FXIII potency value of 43.9 IU/ml), indicating that a plasma standard may be suitable for measuring FXIII concentrates. Estimates of FXIII A2B2 antigen potency for the candidate plasma standard (20/292) showed good agreement between laboratories with a combined inter-laboratory GCV of 4.9% and a combined geometric mean value of 0.98 IU/ml. Estimates of Total FXIII-B subunit potency levels for the candidate plasma standard (20/292) showed good agreement between laboratories with a combined inter-laboratory GCV of 5.4% and a combined geometric mean value of 0.92 IU/ml. Accelerated degradation stability studies carried out after 14 and 17 months storage at elevated temperatures demonstrated good stability with negligible loss (0.001%) in potency at storage temperatures (-20°C). Following agreements by study participants, ISTH/SSC FXIII & Fibrinogen Subcommittee, ISTH/SSC Experts, WHO-ISTH Liaison Group and the SSC Board, the WHO/ECBS established the candidate plasma (NIBSC code 20/292) as the WHO 2nd International Standard for FXIII Plasma with an activity potency of 1.04 IU/ampoule, an A2B2 antigen potency of 0.98 IU/ampoule and a Total FXIII-B subunit antigen potency of 0.92 IU/ampoule, in October 2022.

C. Speaker 3

**Alessandro Casini (University of Geneva, CH).**

**Proposal for an SSC communication: Management of pregnancy in women with hereditary fibrinogen disorders.**

Congenital fibrinogen disorders (CFD) are a heterogeneous group of rare inherited coagulation defects. The spectrum of clinical features is broad, from mild to life-threatening bleeding or thrombosis. Pregnancy is a high-risk clinical situation. It has been reported that pregnant women with CFD may be at increased risk of miscarriages, placenta abruption, thromboembolic events, and post-partum hemorrhage. Management of delivery requires infusion of a fibrinogen concentrate to allow for neuraxial anesthesia and reduce bleeding risk. To date there are no formal guidelines for the management of pregnancy and delivery in women with afibrinogenemia, hypofibrinogenemia and dysfibrinogenemia.

In this communication, we aim to propose expert consensus opinion on the strategy for management of pregnancy and delivery in CFD after reviewing available data.
D. Speaker 4

Zsuzsa Bagoly, (University of Debrecen, HU):

**Inactivation of Factor XIII (Video recorded presentation)**

As opposed to all other zymogenic clotting factors, factor XIII (FXIII) is not a precursor of a proteolytic enzyme but that of a transglutaminase. The inactivation of FXIIIa is still a mystery. Earlier we have shown that polymorphonuclear granulocyte proteases are able to degrade the active FXIII-A subunit (FXIII-A*) in the fibrin clot. Besides this mechanism that can only take place in whole blood, no other biochemical mechanism of FXIIIa inactivation has been reported. A novel mechanism of FXIIIa inactivation is proposed here by us. We found that a spontaneous inactivation of FXIIIa/FXIII-A* can be observed over time, ~50% activity decay occurs in 30 min at 37°C. Using an ultra-high resolution method to study protein stability, altered thermal unfolding of FXIII-A* was found. The inactivation was not driven by protein degradation or excess thrombin, it was not Ca²⁺-dependent. Further details on the exact biochemical mechanism are to be unraveled.

E. Speaker 5

Stephen Baker, (Wake Forest University, USA):

**Thrombin concentration has a more prominent effect on fibrin clot density and porosity than fibrinogen concentration alone.**

Fibrinogen concentration is a well-known determinant of clot density and inversely proportional to clot porosity. In addition, thrombin concentration, shows similar results. How these two in combination effect clot density, porosity, and fractal dimension, a measure related to fiber branching, is less well known. It has been thought that ratio of thrombin to fibrinogen concentrations is the overall determinant of these results. Here, we sought to determine if the product of these two concentrations, related by a power law, was a better determinant of overall clot properties. Using laser scanning confocal microscopy, we imaged clots made by varying thrombin concentration (0.05, 0.1, and 0.2 U/ml) and fibrinogen concentration (0.3625, 0.725, and 1.45 mg/ml) for a total of nine different experimental conditions. Using readily available software, modified for our purposes, we found a relationship for clot density, porosity, and fractal dimension that has significantly better agreement than the ratio of thrombin to fibrinogen concentration alone. We will continue this study, using more physiological concentrations, with the hope of using these findings as a diagnostic tool in the future.
F. Speaker 6

Nicola Curry, (University of Oxford, UK):
Fibrinogen concentrates vs cryoprecipitate therapy for major hemorrhage in trauma.

Trauma haemorrhage is common after significant injury and is often associated with coagulation abnormalities. Fibrinogen is one of the first clotting factors to fall to levels that are too low to effectively support haemostasis, and along with hyperfibrinolysis, is one of the two main changes that is found during bleeding after injury. There are two forms of fibrinogen supplementation that are available for clinical use during treatment of major bleeding - fibrinogen concentrate and cryoprecipitate. This presentation described some of the laboratory and clinical data around the use of these two concentrated fibrinogen replacement therapies and their potential differences. The talk finished by summarising some of the data from the recently completed CRYOSTAT-2 study that evaluated the efficacy of high dose early, empiric cryoprecipitate therapy in 1600 trauma patients.
Meeting Minutes

I. **Call to Order** (Andrew Johnson, PhD)

II. **Agenda Review** (Andrew Johnson, PhD)
   
   Dr. Johnson briefly reviewed how the session would be organized, the availability of the ISTH DEIA policy, the recent widening of the Code of Conduct, and the upcoming availability of open Co-Chair positions including the new Early Career and Reach-the-World Co-Chair options.

III. **Speaker Presentation Notes**

   A. Speaker 1 (Kathleen Freson, PhD)
   
   **Updates for the GoldVariants project to capture genetic variants detected in diagnostic studies.** In 2021 and 2022, 814 and 346 variants have been submitted to the GoldVariants database and all have been transferred to ClinVar. In 2023, 236 variants have been submitted and will be transferred to ClinVar in Q3 2023. These variants can be downloaded via ISTH-GinTH list website (see above). Further submission of single variants can be done via the GoldVariants interface (this website also foresees a bulk upload using an excel spread sheet): https://redcap.isth.org/surveys/index.php?s=MK94LDCXTW. The SSC-GinTH together with the SSC on Physiological Anticoagulants and Thrombophilia has initiated a novel survey about the current practice in phenotypic and genotypic thrombophilia testing. This survey can be accessed via https://redcap.isth.org/surveys/?s=8AWEXTATXN8FJWF7. Question related
to genotyping include inclusion criteria, use of multi-single gene assays, diagnostic rate, management of VUS and submission to variant databases. Two TIER1 genes (KLKB1, BLOC1S5) and one TIER2 gene (NOTCH3) will be added.

B. Speaker 2 (Paula Heller, MD PhD)

*The results of an ISTH supported survey focused on access to genetic and phenotypic diagnosis of inherited platelet disorders (IPD) around the world were presented. The aim of this survey was to map the current situation and address possible regional differences in diagnostic approaches to these rare conditions. There were over 200 responses from 52 countries in all 5 continents which showed limited access to multigene testing for IPD in lower as compared to higher income settings owing to unequal distribution of resources and/or technology. This was coupled with lower access to platelet functional testing for IPD, indicating that parallel efforts should be made to address both shortcomings.*

C. Speaker 3 (Keith Gomez, PhD MRCP FRCPath)

*The ClinGen Coagulation Factor Variant Curation Expert Panel (VCEP) started working on rule specifications F8 and F9 in 2019. The aim was to define criteria for application of the ACMG variant classification rules when assessing F8 and F9 variants. Several rules now have criteria for modification of strength and clear guidance on when they should or should not be used. The rules were submitted to the ClinGen Sequence Variant Interpretation panel who made suggestions. These have been incorporated and a second draft has been submitted. Once the rules have been approved, we will prepare a manuscript for publication. The next project will focus on F7 and F11. We have recruited two new panel members with expertise in these genes.*

D. Speaker 4 (Jorge di Paolo, MD)

*The Variant Curation Expert Panel (VCEP) focuses on adapting the ACMG/AMP criteria to platelet disorders. This effort is supported by the American Society of Hematology within the Subcommittee for Precision Medicine. The first genes curated by the VCEP were ITGA2B and ITGB3. We have 267 ITGA2B and 207 ITGB3 curated variants in ClinVar. We have begun variant re-curation for these genes in 2023 as any variants not meeting pathogenic or benign must be reanalyzed for FDA approval stamp. We are currently piloting GP9, GP1B1 and GP1BB. Initial analyses show: a) Most variants nominated at pathogenic are getting to a pathogenic or likely pathogenic classification b) Many nominated VUS are moving to likely pathogenic or likely benign c) Most nominated benign variants are remaining at that classification of moving to likely benign. Challenges remain on defining PP4 code, the PS4 rules on*
macrothrombocytopenia and how to prioritize a total of 5 genes once these 3 are approved.

E. Speaker 5 presentation (Ana Marin-Quilez, PhD)

Patients with pathogenic germline variants in the RUNX1 transcriptional factor suffer from a familial platelet disorder (RUNX1-FPD), characterized by moderate thrombocytopenia, platelet dysfunction and a high risk of developing myeloid malignancies (AML/MDS) (45% at age 35yr). The use of new sequencing methods is increasing the number of individuals in whom RUNX1 variants are detected. However, half of these variants are of uncertain significance (VUS). Discerning pathogenicity of VUS in RUNX1 is essential for the prognosis and proper clinical management of patients. We have shown that platelet transcriptomics can be a useful tool for the assessment of the pathogenicity of novel VUS in RUNX1, enabling their classification as pathogenic or benign.

F. Speaker 6 (Matt Rondina, MD standing in for Meenakshi Banerjee, PhD)

In recent years, platelet functions have extended beyond thrombosis and hemostasis to include immune and inflammatory roles. Platelets are anucleate yet have a rich and complex transcriptional and translational repertoire comprising of RNAs, miRNAs, lncRNAs, and other subtypes of transcripts. Next-generation sequencing including transcriptome profiling has been widely applied to detect variation in transcript levels attributable to differences in disease states (e.g., inflammation, cancer, etc.), cell type, or gene regulation. The main objective of the STRIDE project, an international collaboration funded by ISTH, is to establish standardized and validated techniques for platelet transcriptomic studies in the field to limit variability between studies and enhance reproducibility of results geared towards discovery and diagnostic efforts. In our study, we show that difference in techniques applied for these kinds of studies including several pre-analytical variables, influences a wide number of parameters that ultimately affect the quantitative and qualitative characterization of the platelet transcriptome.

G. Speaker 7 (Koenraad de Wiselaere, PhD)

The application of platelet transcriptomes to disease case classification was discussed including technical approaches applying autoencoders, and machine learning based approaches and tools to identify predicted potentially pathological splicing events within platelet transcriptomes that may alter and/or truncate protein sequences. The potential scalability of the approach to other transcriptomes and diseases was described.
A study of more than 830 attempted platelet RNA-seq transcriptomes was presented representing the largest such known study. The technical aspects of analysis pipeline were presented along with important QC metrics, and comparison to past ISTH SSC (STRIDE project) results on platelet RNA isolation techniques, identifying additional potential QC approaches including enrichment of mitochondrial RNAs in platelet relative to other cell types, and principal components based analyses to identify additional sample outliers after controlling for white cell (CD45): platelet (ITGA2B) marker ratios. Examples of outcome analyses after data QC were presented demonstrating associations of platelet transcript levels with altered platelet functional results.

A robust discussion carried on in each of the 2 parts of the Session filling the available discussion times.
Meeting Minutes

I. **Call to Order**
Ton Lisman opened the meeting. After welcoming the audience, Dr. Lisman encouraged interested individuals to join the subcommittee by registering at the myisth.com subcommittee page. He also encouraged participants to actively contribute to the discussions during the meeting and to follow-up on these discussions via the myisth.com page or directly by email. Finally, he announced that the SSC subcommittees will be allowed two additional co-chairs. Specifically, one co-chair position for an early career member and one position for a reach the world member will become available. Dr. Lisman encouraged interested individuals to apply – the application process will open shortly.

II. **Agenda Review**
Dr. Lisman announced that the session would start with discussions on 2 guidance documents by this subcommittee, followed by a talk on why implementation of this guidance is complicated. After a talk on animal models of hemostatic changes in liver disease, the remainder of the session would comprise an open discussion with the audience on a research agenda for this subcommittee.

III. **Speaker Presentation Notes**

A. Dr. Lara Roberts presented a summary of the recently published SSC guidance document on Prevention of thrombosis in cirrhosis.
B. Dr. Stephanie Carlin presented a summary of an SSC guidance document on treatment of venous thrombosis and management of atrial fibrillation that is in development. This document is being developed in collaboration with the SSC subcommittee on control of anticoagulation. Dr. Carlin discussed the limited evidence for best practices of therapeutic anticoagulation in patients with cirrhosis, and discussed proposed guidance statements on how to best manage atrial fibrillation in patients with cirrhosis, and how to best treat deep venous thrombosis and pulmonary embolism as well as portal vein thrombosis.

C. Dr. Simon Stanworth discussed reasons why the clinical guidance that has recently been issued by ISTH and a number of other societies (EASL, AASLD, AGA) are poorly adhered to in clinical practice. In general terms, implementation of guidance or guidelines is a difficult process that can be improved by education, reminders given to clinicians in clinical practice, and by audit and feedback cycles. Dr. Stanworth stressed the need for repeated audit cycles and strategies to sustainably alter clinicians’ behavior.

D. Dr. James Luyendyk presented data on mouse models of acute and chronic liver failure and discussed similarities and differences between hemostatic changes observed in mouse models and in humans. A major issue with mouse models of chronic liver injury is that the severity of disease and consequently the severity of hemostatic changes in commonly used models is relatively minor. There thus is a clear need to study hemostasis in mouse models that represent more advanced stages of disease. A commonly used mouse model for acute liver failure (by acetaminophen intoxication) does represent more advanced disease and many similarities between alterations in humans and mice with acute liver failure exist.

E. The chair and co-chairs led a discussion with the audience on projects and topics that should be given priority in this subcommittee. The most urgent questions regard best clinical practices in prevention and treatment of bleeding and thrombosis in patients with chronic liver disease. Studies such as the recently published ProcBleed study, that provided prospective evidence of a low procedural bleeding risk in cirrhosis that was not predicted by routine laboratory tests inform clinical practice, and efforts to collect similar evidence should be given priority. We discussed use of large existing datasets to address relevant questions. There are ongoing UK registry studies on blood component transfusion and prophylaxis that may be helpful, for example. We also discussed similarities and differences between existing guidance documents from different societies. As the differences cause confusion, a joint summary statement endorsed by multiple major societies would be beneficial. Such a summary
statement has been discussed previously, and after the meeting Dr. Lisman will contact colleagues within EASL to try to start working on such a summary document. We also discussed the need for better animal models and animal models for specific clinical situations, notably DIC-associated thrombosis in critical illness which appears related to shock liver and protein C depletion (Transfus Apher Sci. 2021 Apr;60(2):103094), and patients with decompensated cirrhosis and acute-on-chronic liver failure.

IV. **Conclusion/Any additional notes**
ISTH Montreal 2023  
SSC Session –  
Lupus Anticoagulant/Antiphospholipid Antibodies (LA/aPL)  
22 June 2023 16.30 – 18.30 hours EST  
Meeting Room 517

Attendees:  
Professor Hannah Cohen, Chair ISTH LA/aPL SSC Subcommittee/Co-moderator and Speaker  
Professor Katrien Devreese, Co-chair ISTH LA/aPL SSC Subcommittee/Co-moderator and Speaker  
Dr Prabal Mittal, Invited Speaker  
Professor Maria Tektonidou, Invited Speaker (pre-recorded presentation)  
Professor Bas de Laat, ISTH Member, Invited Speaker  
Professor Sam Schulman, Member ISTH Council and Co-chair ISTH LA/aPL SSC Subcommittee, Speaker  
Olivia Ott (medical student), Invited Speaker  
Dr Savino Sciascia, Co-chair ISTH LA/aPL SSC Subcommittee (virtual attendee)  
Audience: N = 357

Meeting Minutes

I. Call to Order  
The meeting was called to order by Professor Hannah Cohen at 1630 hours EST.

II. Agenda Review  
Professor Cohen gave a brief Introduction which included:  
- the mandate and focus of the LA/aPL SSC Subcommittee;  
- stating that the SSC is always looking for new members interested in becoming involved, and that anyone would like to participate in the work of our Subcommittee, or propose a new initiative, should submit an expression of interest form;
- citing the three communications published in JT&H by the LA/aPL SSC Subcommittee since the 2022 ISTH Congress:
  o Vandevelde A et al. Added value of aPS/PT in the workup of thrombotic APS. JTH 2022;20:2136-2150;
  o Cohen H et al. Survey on APS diagnosis an antithrombotic treatment in patients with ischaemic stroke. Other brain ischaemic injury or arterial thromboembolism in other sites. JTH 2023. In press;
- citing the active SSC Subcommittee projects (on SSC Subcommittee Webpage)

Prof Cohen concluded the Introduction by thanking the LA/aPL SSC Subcommittee Co-chairs (Dr M Laura Bertolaccini, Professor Katrien Devreese, Professor Doruk Erkan, Prof Johanna Gebhart, Prof Sam Schulman and Dr Savino Sascia) for their work on the SSC, and the ISTH Team (Cary Clarke, Marie Sahin and Rebekah Parry), for their advice and support through the year.

III. Speaker Presentation Notes
Speaker 1 presentation
Katrien Devreese, Ghent University Hospital, Gent, Belgium
Antiphosphatidylserine/prothrombin (aPS/PT) antibodies in obstetric APS
Currently, laboratory diagnostic criteria of thrombotic APS (TAPS) and obstetric APS (OAPS) are equal and require persistent presence of lupus anticoagulant (LAC), anticardiolipin IgG/IgM, or anti-β2 glycoprotein I IgG/IgM antibodies. Different pathophysiological mechanisms are responsible for the obstetric and thrombotic complications in APS, therefore, we investigated OAPS and TAPS patients separately when studying non-criteria antiphospholipid antibodies (aPL) such as antiphosphatidylserine/prothrombin (aPS/PT) antibodies aPS/PT. In this study, we evaluated in a retrospective multicenter cohort study the role of (isolated) IgG and IgM aPS/PT antibodies. We also investigated whether solid phase assays can substitute LAC testing.
In OAPS, aPS/PT IgG and IgM showed significant odd ratios but not independent from LAC. aPS/PT was more prevalent and showed higher titers in patients with late pregnancy loss compared to patients with early pregnancy loss. In contrast to TAPS, higher aPS/PT titers did not increase the likelihood of having OAPS. Compared to criteria aPL, the added value of aPS/PT testing in the current diagnostic workup of OAPS seems limited. aPS/PT might be useful in specific subsets of OAPS patients. However, future multicentric studies are needed to elucidate the role of different aPL in the risk for the less frequent and most severe obstetric manifestations.

Speaker 2 presentation
Professor Hannah Cohen, University College London, London, UK
**RISAPS (Rivaroxaban in Stroke Patients with APS) trial update**

The 2020 ISTH guidance on the use of direct oral anticoagulants (DOACs) in patients with thrombotic antiphospholipid syndrome (APS) recommended that the potential use of DOACs in APS requires further, appropriately designed, clinical studies, citing the RISAPS trial (ClinicalTrials.gov: NCT03684564) as an example. This randomised controlled, phase IIb, open label, non-inferiority, proof of principle trial is investigating the use of high-intensity rivaroxaban 15mg twice daily versus high-intensity warfarin target INR range 3.0-4.0, in APS patients with ischaemic stroke, transient ischaemic attack or other ischemic brain injury. The rationale for the trial is that: a) the optimal anticoagulation intensity for APS-associated ischaemic stroke is undefined, and high-intensity anticoagulation may be required; and b) rivaroxaban causes a dose-dependent inhibition of factor Xa, with higher peak and trough concentrations with 15mg twice daily vs. 20mg once daily. Of note, higher anti-Xa activity and plasma rivaroxaban levels were required for inhibition of arterial versus venous thrombus in animal models. The primary outcome is the rate of change in brain white matter hyperintensity (WMH) volume on brain magnetic resonance imaging, between baseline and 24 months follow up, WMH being a surrogate marker of ischaemic damage. Recruitment is complete: n = 43 (target 40) and a final study report is anticipated in about 24 months.

**Speaker 3 presentation**

**Dr Prabal Mittal, University College London, London, UK**

**Clinical associations of IgM antiphospholipid antibodies in the prospective APS ACTION Registry cohort**

While the pathogenic potential and clinical relevance of IgG antiphospholipid antibodies (aPL) is well reported, the role of IgM aPL in Antiphospholipid syndrome (APS) is uncertain. A new collaborative project between the ISTH LA/aPL SSC and APS ACTION (AntiPhospholipid Syndrome Alliance For Clinical Trials and InternatiOnal Networking) (supported by a 2023 ISTH SSC Small Grants Award) aims to better define the clinical and pathogenic relevance of IgM aPL. A component of this work is an analysis of the clinical characteristics of patients with IgM aPL in the prospective APS ACTION patient registry, comprising over 1100 patients. Preliminary descriptive findings were presented, focusing on the prevalence and baseline clinical characteristics of patients with an isolated IgM aPL profile. Prevalence was low (~5%), but similar to that of patients with isolated IgG aPL positivity. Approximately 40% of the isolated IgM aPL group were classified as thrombotic APS (with or without obstetric morbidity). An overview of future work was provided, to include further analysis of the APS ACTION registry data, an up-to-date systematic review of the role of IgM aPL in APS, and focused experimental studies on the thrombogenic potential of IgM aPL.

**Speaker 4 presentation**

**Professor Maria Tektonidou**

**Development and validation of a disease activity score in APS**

The development and validation of outcome measures is essential for the appropriate design of observational studies and clinical trials in Antiphospholipid syndrome (APS). The development of a disease activity score, rating specific manifestations from each disease
domain, is challenging in APS due to the multifaceted presentation of both thrombotic and obstetric manifestations, and a wide range of non-criteria features. In addition, disease activity which is in principle reversible should be differentiated from disease damage, which refers to irreversible manifestations of the disease. The development of a disease activity score in APS involves an international collaboration and a multi-phase methodology including established Delphi surveys and nominal group techniques for the item generation and reduction phases, followed by the item weighting and scaling, refinement and validation phases.

Speaker 5 presentations

**Professor Bas de Laat, Synapse Research Institute, Maastrict University, the Netherlands**

**Update on standardization of thrombin generation assays 2.0**

In the past we have collected data on how laboratories perform thrombin generation (TG) which resulted in two manuscripts. Last year we invited participants in a study to investigate whether different methods affect TG results. We included 37 different research groups from all over the world, most of them from Europe and the United States, but also from Brazil, Australia, South Africa & Singapore. Three lyophilized plasma samples (low, medium and high TG) will be sent in order to be tested using the individual laboratory’s own method and a standardized prespecified protocol. We are currently waiting for the lyophilized plasma samples to be ready, anticipated in September/October 2023, following which the samples will be sent to the participants. Thirty-nine laboratories have indicated that they would like to participate: 20 from Europe, 14 from America, 3 from Australia, 1 from Singapore and 1 from South Africa, with the most, the last group joined 2 weeks ago. (After the presentation, an additional group, Belgium, requested to participate).

**Professor Bas de Laat, Synapse Research Institute, Maastrict University, the Netherlands**

**Epitope specificity of lupus anticoagulant-causing prothrombin antibodies**

Of all antiphospholipid antibody (aPL) assays, lupus anticoagulant (LAC) is best related to thrombosis and pregnancy loss. A LAC can be caused by either anti-beta2-glycoprotein I antibodies or antibodies with different specificity. Several years ago, we showed that prothrombin antibodies have a different effect on coagulation but also cause LAC. In this study we show the existence of different populations of anti-prothrombin antibodies and their epitope specificity in relation to LAC-causing antibodies. We found that anti-prothrombin antibodies bind to fragment 2 of prothrombin and can activate platelets. We have developed a specific assay for the detection of these antibodies and would like to confirm our results in a multicenter study.

Speaker 6 presentation

**Registry on augmented antithrombotic treatment regimens for patients with arterial thrombotic APS**

**Professor Sam Schulman, McMaster University, Canada**

Management of patients with arterial antiphospholipid syndrome (APS) presents a substantial challenge. Their risk of recurrent events, the most commonly reported being
ischemic stroke, is about 22% during 2 years on an anticoagulant or an antiplatelet agent. The strongest EULAR recommendation for antithrombotic treatment is for vitamin K antagonist (VKA) (Grade B). The question is whether combined antithrombotic therapy, either with VKA plus low-dose-aspirin (LDA) or with dual antiplatelet therapy (DAPT) for patients with arterial APS can improve the outcome. The risk of bleeding in these patients appears to be low in published studies and meta-analyses. Our Subcommittee therefore initiated a registry with the main intention to gather data on patients with arterial APS being treated with VKA plus LDA or with DAPT after a recent arterial event with 2-year prospective follow-up. Patients treated with VKA alone are also included for comparison. Data are entered into ISTH RedCap. So far 16 patients (6 centers) have been entered, 5 males, 11 females, median age 49 (35-53), 14 had ischemic stroke. Therapies used are VKA+LDA, DAPT, and VKA alone (INR 2-3).

Speaker 7 presentation

Olivia Ott (medical student), Coagulation Center and Coagulation Research Center, Cardioangiology Center Bethanien Hospital, Germany

Prospective observational study to evaluate a possible change in APS Antibody profiles after COVID-19 Infection or Vaccination (APSantiCo-study)

After the start of the COVID-19 pandemic in early 2020 the extent to which COVID-19 infections and/or COVID-19 vaccinations alter antiphospholipid antibodies (aPL) in patients with thrombotic antiphospholipid syndrome (APS) was not clear. Therefore, eighty-two patients with confirmed thromboembolic APS were included in a prospective non-interventional trial assessing blood parameters including aPL prior to and after COVID-19 vaccination and/or COVID-19 infection. No increases in aPL in the total study population were detected and only one arterial thrombotic event was diagnosed. The data suggest that COVID-19 infections and/or vaccinations do not adversely impact on the clinical course of anticoagulated thrombotic APS patients.

IV. Conclusion/Any additional notes

Prof Cohen thanked all the Speakers for their presentations and the audience for their participation in the Session.

The session was well attended and appeared to be well received.

Hannah Cohen
Chair, ISTH LA/aPL SSC Subcommittee
30 June 2023.
Models of Thrombosis and Hemostasis

**Chairperson:** Laura Gutiérrez (Peter Gross substituted for the in-person events at Montreal 2023)

**Co-Chairs:** Peter Gross, Beatrice Hechler, Olivia R. Palmer, Viviana Clavería, Steven Grover and Frederik Denorme.

**ISTH 2023 SSC Meeting (Palais de Congress, Montreal)**

27th June 2023 (Room 520)
In-person only session.

After an introduction, the substituting chair, Peter Gross, presented an overview of projects and their co-leads.

The success of the Interactive Webinar by Dr. Matthew Brooke from NC3Rs in the UK who spoke about the new ARRIVE guidelines on animal research reporting was highlighted. The audience was reminded to check MyISTH for future surveys on learning needs in this area.

Steven Grover spoke briefly about his project and the forthcoming launch of a questionnaire on inferior vena cava stenosis thrombosis preclinical model, the website is not ready to be distributed yet. (see an update of current Projects below).

**Session Program:**
The program theme this year was Humanized Murine Models. It contained two parts, the first one focusing on von Willebrand. The second part covered humanized murine models of sickle cell disease and GPVI. The selected participating speakers offered high quality insights on respective subjects.

**FIRST PART – vWF:** Moderators, Frederik Denorme and Viviana Clavería
   Dr. Alessandro Zarpellon, USA
2. Humanized mouse models of von Willebrand disease
   Dr. Peter Lenting, France
There were five questions from the audience and three additional questions from the moderators. The questions were equally directed to both speakers.

SECOND PART: Moderators, Beatrice Hechler and Steven Grover.
3. Sickle Cell Disease humanized mice: liver-to-lung microembolism – thromboinflammation
   Dr. Prithu Sundd, USA
4. Humanized GP VI mice
   Dr. Martine Jandrot-Perrus, France

There were 6 questions from the audience and 3 additional questions from the moderators. Questions were directed to both speakers.

The speakers and the audience were thanked, and the meeting was adjourned by Peter Gross

Publications:

In preparation:
   - Platelet Proteomics (still in preparation, see below current projects).

Current Projects:
All new projects are presented at every ISTH congress since 2020 (Virtual), and a brief update was given at the ISTH 2023 (Montreal). Below the project descriptions and updates, which are all characterized by being executed in two phases: bibliographical (to assess the state-of-the-art, define demands and the experimental phase) and experimental (standardization).

Current Projects are registered and accessible at the SSC website page. A brief update is given below:

1. Platelet proteomics – clinical applications project began: 2022 project conclusion: TBD
   See minutes from ISTH 2019, especially ISTH 2022, for an overview. In brief, the platelet proteome profile has enormous potential, as a source for biomarker discovery, with prognostic and diagnostic value, at the same time as providing information on
health/disease status. In an effort to set the current status of the technique in the field, we generated a working team in collaboration with other SSCs.

Coordinator: Laura Gutiérrez.
Participants: Collaboration with SSCs of PLT Physiology and Predictive/Diagnostic Variables.

We had several meetings with members of the other SSCs, which later expanded to a rich list of collaborators, some of them external to the SSCs. These are updated participants of the working group, which include senior and junior researchers:
Samuel Tassi-Yunga and Joseph Aslan, Ángel García, Paulina Szklanna and Patricia Maguire, Johan Heemskerk, Matthew Rondina, Patricia Martínez-Botía and Laura Gutiérrez, Hervé Falet and Marie Lordkipanidze, and Kerstin de Wit.
We have a definitive draft of the revision.

UPDATED Chronology:
- Current Status: Joseph Aslan is still working on the final draft after comments were received from Johan Heemskerk, Angel Garcia and Patricia Maguire.
- We hope to conclude it this year, as agreed on conversation prior ISTH 2023.

2. Evaluating procedural and reporting variability in the inferior vena cava stenosis thrombosis model project began: 2022 project conclusion: TBD

Coordinator: Steven Grover
Participants: Viviana Clavería and Frederik Denorme, who suggests also to invite members of the SSC on Vascular Biology.

The murine inferior vena cava stenosis model of venous thrombus formation is a commonly used procedure to investigate mechanisms of venous thrombus formation and resolution. Studies using this model have provided important insights into the contribution of a number of pathways including coagulation and immune cell mediated processes. As with many preclinical models the specific procedure used to induce thrombus formation with this approach varies between investigators.

UPDATED Chronology:
First, a questionnaire is going to be prepared to have the opinions of experts of the ISTH community. This project was presented at the SSC session ISTH 2022.

The questionnaire has been elaborated and approved by the SSC, Steven Grover has initiated contact with Marie Sahin, as to launch it online, via My ISTH Community.

3. Evaluating procedural of mouse models of platelet depletion and transfusion for the in vivo assessment of platelet function project began: 2022 project conclusion: TBD

Coordinator: Beatrice Hechler
Participants: Laura Gutiérrez, Viviana Clavería.

UPDATE / falling??

4. Cellular Models of Megakaryopoiesis and Platelet Production, including co-culture and organoids project began: 2022 project concluded: TBD

Coordinator: Beatrice Hechler.
Participants: Laura Gutiérrez, external collaborators.

UPDATE / falling??

Other Proposed Projects:

DIDACTIC / Teaching Section:
By all SSC CoChairs: to elaborate Model Cards, visual and schematic, of different models, the ones they have expertise on, or the ones that are frequently used, considering, in vivo, in vitro, molecular, and trying to engage on computational.
These cards will be available on our page, linked to a “blog” option, so readers/users can ask questions, share troubleshooting, etc, even suggest the elaboration of other Model-Cards, etc.

After a year, a report will be written with all feedback obtained.

Commented [L1]: ANY NEWS, Steven??
Commented [L2]: Beatrice, what is your view on this? Something to keep on doing as collaborator, or shall it fall?
Commented [L3]: Beatrice, Same comment as above. What is your view on this? Something to keep on doing as collaborator, or shall it fall?
Commented [L4]: See if you like this proposal, and maybe name the models you could reflect on CARDS.
Pre-clinical models of Pulmonary Embolism
Coordinator: Peter Gross.
Participants: Olivia Palmer.
This project, proposed by Peter Gross, is at the core of the interests of our SSC. This was represented on the SSC meeting, with the talk by Tetsuya Hara.
Update: It will be discussed on our next SSC meeting, to be held virtually at the end of September or beginning of October.

Update: co-chairs are rotating, this project fails.

Preclinical Models of Stroke
Coordinator: Frederik Denorme
Participants: (to be determined in our next SSC meeting, including external collaborators).

Stroke is a leading cause of mortality and permanent disability, impacting over 15 million people annually. Strokes are caused by a blood clot (ischemic stroke; 90%) or a brain bleed (hemorrhagic stroke; 10%), in either case, treatment options are limited. This highlights an urgent need for standardized models that can aid in the discovery and validation of novel treatment strategies. As hemostatic abnormalities are nearly always at the root of stroke, this is a relevant topic of interest for the ISTH - Models of Thrombosis and Hemostasis SSC. The goal of this project is to provide the ISTH community an overview of the available stroke models with their strengths and weaknesses, and their applicability depending on the research question that needs to be addressed. This will be published either as a Blog Post or Review Article. A second aim is to identify areas where models need standardization to improve reproducibility.

At the ISTH 2022 in London, Dr. Sara Martinez de Lizarrondo was the first invited speaker discussing this topic with a focus on rodent models of ischemic stroke. Dr. Martinez de Lizarrondo highlighted thrombotic stroke models, used to discover new (pro-)thrombolytic drugs, as well as models of ischemia/reperfusion injury, used to model the inflammatory cascade after ischemic stroke. She also presented on several behavioral tests used to measure stroke outcomes and the difficulties associated with interpreting these results. Finally, the need to take into account comorbidities in preclinical stroke models was brought up. It is believed that including comorbidities in preclinical studies might improve translation to the stroke clinic, however this remains to be evaluated.

Commented [L5]: I assume this is correct, Peter and Olivia. Or still a chance to make a Model CARD for the TEACHING section still?

Commented [L6]: Any updates on this? Shall we have MODEL CARDS, and start form that?
A Shear-Induced-Platelet-Aggregation (SIPA) point-of-care assay for thrombolytic activity characterization in patients.
Coordinator: Viviana Clavería
Participants: to be determined in our next SSC meeting.

In myocardial infarction (MI), platelet aggregation develops in the coronary artery under pathological conditions of high shear blood flow forming a SIPA clot. MI is one of the main causes of death in the world. Because of the high mortality records, there is a great demand for finding methods and medical devices for diagnosis, and prevention of this disease. Here, we propose the use of a SIPA point-of-care (POC) assay for thrombolytic activity characterization in patients. SIPA is a model of thrombosis relatively recently developed and by this assay we are intended also to validate it using our assay with this project we aim to validate this assay. Our assay has been built based on clots formed by platelet aggregation (SIPA clot), therefore relating our system to arterial thrombi formation. Our central hypothesis is that we can predict the risk of patients for having a MI using our POC assay, evaluating the time that it takes to for a patient to form a thrombus under high shear flow conditions (called occlusion time (OT)). Currently, the coefficient of variation of our POC assay is less than 10%, tested on 10 healthy subjects. Nevertheless, the “healthy” thrombolytic OT, as well as the intra, and inter-variability needs to be obtained by getting the OT from over more than 100 healthy subjects. OT of an abnormal population will be obtained by testing 50 patients that just had MI without having previously taking any drug or anticoagulant.

Objective:
The main objective of this work is to develop our SIPA point-of-care assay and validate it under a clinical trial by measuring the OT on extreme populations that has developed (healthy) or not MI.

Projects proposed by new co-chairs, shall be defined during the year.

Co-chair rotations:
This year, we have rotations of three co-chairs: Peter Gross, Beatrice Hechler and Olivia Palmer. I have interviewed the interested people that contacted us last year, Dr. Ahmed Ghareeb (Egypt) and Dr. Tessa Barret (USA), and they still wish to join us. Furthermore, we had an additional application this year, Dr. Baranidharan (India), and I have interviewed him as well. My impressions...
are positive for the three candidates. I have asked the three candidates to send a brief Biosketch and interest document, that I can reboot to all SSC co-chairs for evaluation, in order to have a consensus on their incorporation.

**SSC Internal Meeting:**
End September 2023 or beginning October 2023, we will held a virtual meeting, in order to brainstorm on the new projects proposed, specially the “teaching” project, on the status of ongoing projects, and the potential incorporation of the new co-chairs.

**OBSERVATIONS:** the collaborative efforts are very enriching and interest, but require coordination, and things have progressed rather slowly (i.e. Platelet Proteomics Project, Platelet Transfusion Models, Megakaryocyte Culture Models). We will conclude the Proteomics Project, which I coordinate, however, the other projects were led by one co-chair that rotates. This made me think of other activities to develop by the SSC, more dynamic, with a direct reaching-out perspective, as some of the interactive bibliographic projects, will probably not be executed as planned. Since all the work is voluntary, and all co-chairs have their own agenda, sometimes the path takes a slow rhythm. I hope in this last year as Chair-person, I can accomplish some of the planned activities, and engage the new co-chairs into fruitful projects that may be of use to the ISTH Community.
Physiological Anticoagulants and Thrombophilia SSC
June 24, 2:30-4:30pm
Meeting Room 510

Attendees:
- Chair - Vera Ignjatovic
- Co-chair - Javier Corral
- Co-Chair - Alan Mast
- Co-Chair - Gary W. Moore
- Co-chair - Christelle Orlando
- Regular members of the PAT SSC
- Numerous other attendees – the session was extremely well attended.

Meeting Minutes

I. Call to Order
As a congress session designed to update on our projects and educate the audience as to the most important topics in this space, rather than a regular PAT SSC business meeting, this session started by an introductory presentation by the SSC Chair, Dr. Ignjatovic, followed by presentations outlined in the agenda below. Dr. Ignjatovic concluded the session following the second Q&A session.

II. Agenda Review

<table>
<thead>
<tr>
<th>First Name</th>
<th>Last Name</th>
<th>Credentials</th>
<th>Role (Moderator/Speaker)</th>
<th>Organization</th>
<th>Presentation Start Time</th>
<th>Presentation End Time</th>
<th>Presentation Title/Topic</th>
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</thead>
<tbody>
<tr>
<td>Vera</td>
<td>Ignjatovic</td>
<td>PhD</td>
<td>Moderator</td>
<td>Johns Hopkins All Children's Hospital</td>
<td>14:30:00</td>
<td>14:40:00</td>
<td>Session Welcome</td>
</tr>
<tr>
<td>Zsuzsanna</td>
<td>Bereczky</td>
<td>MD, PhD</td>
<td>Speaker</td>
<td>University of Debrecen</td>
<td>14:40:00</td>
<td>14:50:00</td>
<td>Antithrombin deficiency update</td>
</tr>
<tr>
<td>Riten</td>
<td>Kumar</td>
<td>MD, PhD</td>
<td>Speaker</td>
<td>Boston Children's Hospital</td>
<td>14:50:00</td>
<td>15:00:00</td>
<td>Inherited Anticoagulant deficiencies and VTE in children</td>
</tr>
<tr>
<td>Eriko</td>
<td>Morishita</td>
<td>MD, PhD</td>
<td>Speaker</td>
<td>Kanazawa University</td>
<td>15:00:00</td>
<td>15:10:00</td>
<td>FV Kanazawa (clinical/lab)</td>
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<tr>
<td>Rinku</td>
<td>Majumder</td>
<td>PhD</td>
<td>Moderator</td>
<td>LSU Health</td>
<td>15:10:00</td>
<td>15:20:00</td>
<td>Q&amp;A</td>
</tr>
</tbody>
</table>
### Speaker Presentation Notes

#### A. Zsuzsanna Bereczky

**Antithrombin deficiency registry update**

As antithrombin deficiency (ATD) is a rare disease, it is difficult to establish guidelines and standardized approach on laboratory diagnosis and patient management. Current laboratory diagnostic methods have considerable limitations, and the major issues are as follows. There is a heterogeneity of the sensitivity among the commercially available functional assays, especially in
case of type II defects. Major factors are heparin concentration and ionic strength, which may influence the performance of these assays. Moreover, a standardized and widely accepted assay for the detection of β-AT is lacking, despite it is suggested that the altered amount of β-AT is responsible for the clinical and laboratory heterogeneity of ATD and it may have an impact in different cardiovascular diseases. Commercially available plasma standard for β-AT is also missing. There are unusual forms of ATD, as SERPINC1 variants which affect N-glycosylation or transient ATD, which are not detected by routine functional tests, or congenital disorders of glycosylation which lead to ATD. It can be concluded that method development in ATD is warranted.

Among clinical issues the administration of antithrombin concentrate and NOAC are the most emerging ones requiring large data collection.

The aim of establishment of an international ATD registry was to collect large amount of data from patients all over the world. There are n=13 participant institutes registered and n=644 cases have been uploaded, so far. We are still seeking for more participants; registration can be done at the RedCap platform (https://redcap.isth.org/surveys/?s=J4YA4E7AFN).

B. Riten Kumar

Inherited anticoagulant deficiencies and VTE in children

While historically considered rare, venous thromboembolism (VTE) is being increasingly recognized in children. Administrative database studies from the United States estimate a 130-200% increase in the rate of VTE among hospitalized children over the last two decades. Despite this increase, more than 90% of thrombotic events in children are provoked by transient risk factors like central venous lines, trauma, and infection. In this evolving landscape of pediatric VTE, the relevance of congenital thrombophilias including natural anticoagulant deficiencies on pediatric VTE is unclear. In this session, we will investigate the impact of congenital deficiencies of antithrombin, protein C and protein S on the risk of incident and recurrent thrombosis in children. We will additionally discuss the clinical presentation and management of children with natural anticoagulant deficiency and VTE. Lastly, we will review evolving data on the genotype-phenotype correlation of congenital AT deficiency and the clinical management of severe protein C deficiency in children.

C. Eriko Morishita

Factor V Kanazawa (Clinical/Lab)

We have identified a novel FV variant that exhibits APCR through a different mechanism than FV Leiden. Our patient was a 42-year-old Japanese male who presented at our hospital for recurrent DVT since his 20s. FV activity and antigen in the patient were 6% and 32%, respectively. The APC sensitivity ratio obtained in patient’s plasma was similar to that of FV Leiden patient.
Direct sequencing of the patient identified compound heterozygous variants of F5 gene, Tyr1961Cys, and FV Asn1982-Ser1983 del which has been already reported to be a loss-of-function variant. Therefore, we hypothesized that FV-Y1961C could be the cause of thrombosis, and named it FV Kanazawa.
Recombinant FV Kanazawa was expressed in HEK293 cells. We found that FV Kanazawa was significantly defective on APC-induced inactivation and impaired FV cofactor activity for APC, similar to FV-Nara.
Tyrosin1961 is located in the C1 domain, in proximity to the phospholipid binding sites. We speculate that FV-Kanazawa was disturbed for phospholipid interaction, consequently resulting in impaired FVα susceptibility and FV cofactor activity for APC, similar to FV Nara.

D. Alan Mast and Javier Corral
Clinical Impact of new rare thrombophilia interactive session
This interactive session focused on the experience and thoughts of the audience in relation to rare thrombophilia from the diagnosis perspective. The session was run using the interactive platform Kahoot, and more than 150 audience members participated actively in this part of the session.

E. Elena Campello presenting instead of Paolo Simioni
Pros of thrombophilia testing
The clinical utility of a test is the ability of the test to improve clinical outcome. Thrombophilia testing improves clinical outcome in several settings. 1) As the heritability for venous thromboembolism (VTE)is estimated to be as high as 60% and genetically determined defects collectively lead to at least a third of cases of VTE, thrombophilia testing allows clinicians to explain at least in part the etiology of the thrombotic event to patients worried about it. 2) In some case it can influence initial management of VTE (i.e. antithrombin and severe protein C deficiencies). 3) It is of the utmost importance in the assessment of the overall patients’ VTE recurrence risk in the clinical decision making for secondary prevention. 4) According to the latest ASH guidelines, it can influence secondary prevention strategies in patients with VTE provoked by major (non-surgical) or combinations of minor risk factors. 5) It is also important for guiding primary prevention strategies in patients with minor provoking risk factors and also in patients with cancer and low-intermediate risk.

F. Beverley Hunt
Cons of thrombophilia testing
Thrombophilia testing is widely asked for and causes confusion and anxiety in health care professionals and patients. Doctors from multiple area from fertility and recurrent miscarriage clinics, cardiology and stroke clinics erroneously request thrombophilia testing. The content of thrombophilia testing is not agreed internationally and long discredited assays such as MTHFR are still included in some centres. It’s utility is poor, it is not “screening” performing inherited
thrombophilia in those with a recent clot and a strong family history yields only 50% pick up of an underlying known thrombophilia. I will argue that access to testing needs to be greatly restricted!

**G. Christelle Orlando**

**How phenotypic testing informs decision making for genotypic testing**

Patients with deficiencies of natural anticoagulant proteins such as antithrombin, protein C and protein S, are usually identified by phenotypic tests performed on plasma. The congenital nature of the deficiency can be confirmed using molecular analysis of the respective genes. During the last decade, molecular techniques have evolved from single-gene Sanger Sequencing to high-throughput multi-gene sequencing panels. This has led to the discovery of new genetic variants, some of which the pathogenicity remains unclear (VUS, variants uncertain significance). The multi-gene sequencing approach can also result in unexpected findings of variants in other coagulation genes in addition to the gene of interest.

The presented study aims to obtain additional insights into the current practice of thrombophilia testing and more specifically to understand if and how coagulation laboratories place genetic testing in their diagnostic workflow. Additionally, it is currently unknown how laboratories react on the found gene variants, particularly VUS. The results of this study will inform the design of a subsequent study that will undertake wider phenotypic and genetic testing to assess the contribution of genetic testing to thrombophilia diagnosis.

**H. John Hogwood**

**Summary of Collaborative Study to establish the 3rd International Standard for Protein S, Plasma**

The WHO International Standard (IS) for Protein S, Plasma is used to determine protein S activity in patient samples who present with thrombophilia. This global reference material, currently the 2nd IS 03/228, required a replacement due to stock levels running low. An international collaborative study, involving 21 laboratories including diagnostic manufacturers, was carried out to assign value to a replacement against the current material. This study determined the suitability of the proposed replacement with inter-laboratory geometric coefficients of variation of 4.5% for functional, 5.2% for free antigen and 3.5% for total antigen. It is proposed that the replacement material, coded 22/202 be established as the 3rd IS for Protein S, Plasma with the following values assigned to it: **functional activity – 0.71 IU/ampoule, free antigen – 0.83 IU/ampoule and total antigen – 0.88 IU/ampoule.**

**IV. Conclusion/Any additional notes**

This was an extremely well attended session with many attendees being forced to stand due to a lack of seating space – as the session was completely packed out. The presentations drew numerous questions from the audience and it was absolutely clear that the work of the PAT SSC is very much in line with the needs of the ISTH community.
The interactive component of the session ran smoothly, although Dr Corral was personally responsible for purchasing the Kahoot license upgrade to ensure that all of the audience attending the session could participate. The PAT SSC urges the ISTH organizers to ensure that an access to a uniform, conference-wide interactive platform is provided for ISTH 2024 and beyond.
Attendees:

Name, ISTH Title/Role: Jean M Connors, SSC Chair, moderator
Name, ISTH Title/Role: Jerrold Levy, SSC Co-chair, moderator, speaker
Name, ISTH Title/Role: Kenichi Tanaka, SSC Co-chair, moderator
Name, ISTH Title/Role: Alfonso Tafur, SSC Co-chair, moderator
Name, ISTH Title/Role: Corinne Frere, SSC Co-chair, speaker, moderator

Meeting Minutes

I. Call to Order
   Jean Connors introduced the session and reviewed the agenda

II. Agenda Review

III. Speaker Presentation Notes

SSC 11.2 - CURRENT PROJECTS UPDATE on ISTH Guidelines for Anticoagulation in COVID19: Sam Schulman

Sam Schulman discussed the status of the updates for the published ISTH Guidelines for Antithrombotic Treatment in COVID-19 (JTH, 2022). As a large number of studies have been published since the the ISTH guidelines came out, all PICO questions in the original document will be updated. Additionally, information on the diagnosis and treatment of VITT will be included. Sam described the work in progress and timeline for completion.

SSC 11.3 - Anticoagulation for ECMO 1 and 2: Corinne Frere

Corinne Frere gave both planned presentations on the recently published SSC on Perioperative and Critical Thrombosis and Hemostasis Guidance for anticoagulation in ECMO (JTH, 2023)
Despite significant advances in the technology of extracorporeal membrane oxygenation (ECMO), systemic anticoagulation is still required to prevent clotting in the pump, tubing, and oxygenator. Nevertheless, anticoagulation is challenging in patients supported with ECMO due to bleeding concerns. Evidence-based consensus is paramount to support daily clinical decision-making. The Scientific and Standardization Committee on Perioperative and Critical Care Hemostasis and Thrombosis of the International Society on Thrombosis and Hemostasis has recently issued guidance for anticoagulation in adult patients supported with ECMO. The purpose of this guidance is to provide clinicians with practical advice on anticoagulant agent selection, anticoagulant dosing, and anticoagulation monitoring options.

**SSC 11.8 - PAUSE-2 pilot updates: Jim Douketis**

**SSC 11.9 - PAUSE-ER study updates: Deb Siegal**

Jim Douketis gave the PAUSE-2 pilot updates and Deb Siegal gave the PAUSE-ER updates. The PAUSE research program aims to advance knowledge and inform clinical care for patients who are receiving a direct oral anticoagulant (DOAC) and require a surgery/procedure. PAUSE-2 pilot is an ongoing randomized controlled trial comparing 2 strategies for the perioperative management of DOAC-treated patients who require a high-bleed-risk surgery and/or neuraxial anesthesia: PAUSE strategy vs. ASRA (longer DOAC interruption) strategy, with immediately pre-operative DOAC levels as the primary outcome. PAUSE-ER is an ISTH-funded and recently-completed prospective observational study assessing management practices and clinical outcomes in DOAC- and VKA-treated patients who require an urgent surgery.

**SSC 11.10 - Heparin Resistance: Jerrold Levy**

Jerrold Levy discussed the current SSC project for defining heparin resistance.

Unfractionated heparin (UFH) is the anticoagulant of choice in ICU and critically ill patients. However, a large interindividual variability of its anticoagulant effect is common, and during the COVID-19 pandemic, heparin resistance was increasingly reported in ICU patients. Heparin resistance could be defined as UFH failure to achieve a specified anticoagulation level despite our literature search and report on what is considered to be an considered resistance. Current definitions commonly used are inappropriate since they omit body-weight adjustment, other clinical settings, drug target values, and extracorporeal circuits. In the ICU, heparin resistance is often invoked when UFH requirements continuously increase or when UFH doses which are considered adequate fail to achieve the desired aPTT therapeutic range. However, chromogenic anti-Xa assays are also increasingly used as sole or combination testing to evaluate heparin effects and potential resistance. Our current survey will hopefully better define this concept for clinical considerations.
IV. **Conclusion/Any additional notes**
The session was very well attended with lively question and answer sessions and discussions, especially about the in-progress updates to the SSC COVID-19 antithrombotic guidelines and the SSC guidance for anticoagulation in ECMO. We look forward to presenting updates on the works in progress and presentation of new projects by the Subcommittee on Perioperative and Critical Care Thrombosis and Hemostasis at ISTH 2024 next year.
- Welcome and Introductory Remarks (Tamam Bakchoul, Germany)

The session started with an introduction by Tamam Bakchoul who gave an overview of current projects in Platelet Immunology SSCs and briefly introduced the session program.

- ITP Session Moderated by TB and H Al-S

Prof. Donald Arnold discussed the diagnostic utility of platelet autoantibodies and a new Predict-ITP clinical scoring system in the diagnosis of immune thrombocytopenia. This included recent meta-analysis data regarding the excellent specificity and inadequate sensitivity of direct glycoprotein-specific platelet autoantibody assays as well as the initial promising data regarding the utility of the Predict-ITP score, which integrates data regarding a patient's observed platelet count variability, development of bleeding, and lowest platelet count measured, among other variables, to predict the likelihood of an ITP diagnosis.

Dr. Catherine Broome discussed neonatal Fc receptor antagonism for the treatment of immune thrombocytopenia, including published phase 2 data for rozanolixizumab, the recently presented phase 3 data on efgartigimod, and the early data on nipocalimab and batoclimab. She additionally reviewed the various mechanisms by which antagonism of the neonatal Fc receptor may be effective in the treatment of humoral autoimmune disease. The data she presented highlighted the potential promise of this new class of therapeutics in the treatment of ITP, demonstrating safety and efficacy in a heavily-pretreated population of patients.

Dr. Hanny Al-Samkari discussed recent and historical data published regarding persistent isolated mild thrombocytopenia (persistent isolated platelet counts between 100-149 k/uL). The data presented reported high rates of progression of these patients to full-blown immune thrombocytopenia as well as hematologic malignancy over extended follow-up (of over 20 years) as compared to matched control subjects. He recommended the ISTH Platelet Immunology SSC subcommittee launch a clinical guidance statement initiative regarding the counseling and management of these patients, given the dramatic heterogeneity of current clinical practice.
Pr Claire Pouplard presented the results of the first external quality assessment carried out with 5B9 for functional HIT tests. 19 laboratories in France and Belgium participated in this study, and platelet aggregation tests were performed by 16 centers. HIPA, FC, HIMEA and HIPA were performed by one center each, and SRA was performed in two centers. 2 laboratories performed two different tests. It is interesting to note that the results obtained with HIMEA, FC, HIPA and SRA were always in accordance with the expected results. On the contrary, PAT findings were more variable. Two vials contained very low levels of 5B9 (10 microg/ml) and a negative result was expected. However, 31% and 18% of findings were positive with PAT during the first and second investigations respectively. In contrast, a negative finding was never reported for the two vials containing high levels of 5B9 (400 microg/ml).

The TAP procedures of each center were analyzed and many differences were highlighted, emphasizing the need to draft SSC recommendations for functional testing and specifically for TAP. A survey on functional testing will be put online at the beginning of July on the ISTH website, and the results will be very useful in drafting this text. The key take-home messages from these talks were the significant role of procoagulant platelets in thrombus formation, their involvement in HIT, and their potential as diagnostic markers for HIT.

Dr Alessandro Aliotta gave a presentation on procoagulant platelets, the mechanisms of their generation, identification, and clinical relevance. The speaker highlighted that procoagulant platelets play a crucial role in various bleeding or prothrombotic diseases. The talk emphasized that HIT-antibodies mediated activation of platelets mimic and share similarities with the signaling induced by GPVI activation, giving valuable insights of procoagulant platelets into the pathogenicity of HIT and potentially identify novel diagnostic tool.

Dr Jan Zlamal focused on procoagulant platelets in HIT and their impact on thrombus formation. The speaker discussed how HIT antibodies activate platelets through FcγRIIA receptors leading to the formation of procoagulant platelets and he directed towards the diagnostic potential of procoagulant platelets. The presentation highlighted the crucial role and the contribution of the procoagulant platelet subpopulation to the pathogenesis of thrombosis in HIT.

Associate Prof. Vivien Chen explored the potential diagnostic value of procoagulant platelets in HIT. The speaker discussed how flow cytometry could detect and characterize procoagulant platelets generated by HIT plasma. The presentation highlighted that optimising platforms including donor selection, could lead to rapid and accurate diagnostic approaches to differentiate HIT from other causes of thrombocytopenia.
- Concluding remarks (Tamam Bakchoul, Germany)

Dr Bakchoul thanked the speakers for the excellent talks and the attendees for their active participation and helpful input. After summarizing the key notes of the session, Mr Bakchoul proposed is to generate a guidance document on the methods to detect platelet activating antibodies in patients with HIT and ITP.

- Discussion and question period

All panel members

In terms of attendance, we estimated more 200 attendees. Discussion from the audience was active and lively when interactions were solicited. Many participants emailed speakers with follow-up questions or expressed desire to participate in the ongoing SSC projects

Joint project of the SSC PLT Physiology and SSC PLT Immunology:

Leader Dr Ruchika Sharma

Summary of the talk:

The platelet physiology SSC and platelet immunology SSC collaborated on a joint project for establishing consensus guidelines for platelet function testing in patients with thrombocytopenia. The flow cytometry part of the project was presented by my collaborator and I presented the platelet aggregometry part of the project. The process for this was reviewed. After project conception and approval, an expression of interest form was opened at ISTH webpage. A second survey was circulated regarding pre-analytical, analytical, post-analytical and performance aspects of aggregometry for thrombocytopenic patients in 2022. 34 responses was received which helped identify areas of disagreement and paved the way for the focus group discussion. Two focus groups of experts in the field of whole blood aggregometry (WB focus group) and light transmission aggregometry using platelet rich plasma (PRP focus group) was gathered and the 2 focus group discussions were held in March 2023. The preliminary results of the survey and focus group discussions was summarized in the presentation.

With regards to platelet count threshold, there were significant discrepancies among survey participants. The PRP focus group favored the use of 75,000/uL as the platelet count threshold below which results are unreliable. However, the group had consensus that lower platelet counts are acceptable in certain specific conditions. For whole blood aggregometry, a threshold of 50,000/uL was recommended. With regards to use of control sample, PRP focus group recommended use of assay (instruments/reagents) control; the whole blood group recommended control for CHRONO-LOG® but not for Multiplate®. With regards to using a platelet count adjusted control, the PRP focus group discussed using platelet-count adjusted control with autologous
platelet poor plasma in addition to the unadjusted control. The WB focus group recommend running the patient sample without dilution and did not recommend any adjustment to the control. With regards to agonists, the PRP focus group recommended that laboratories should develop local reference ranges using previously published literature since majority of the agonists become unreliable at counts below 100,000/ uL. However the group recommended considering high concentration of collagen and low/high concentrations of ristocetin for ruling out specific disorders (BSS, type 2B von Willebrand disease). WB focus group did not modify agonists or concentrations, but recommended use of low and high concentrations of ADP to account for endogenous ADP release from the platelets and red cells. With regards to ATP secretion, the PRP focus group had concerns regarding limited data in thrombocytopenic samples and poor reproducibility of ATP secretion, therefore the group did not recommend the evaluation of ATP secretion in thrombocytopenic patient samples. The WB focus group did not modify existing protocol for evaluation of ATP secretion in thrombocytopenic patients, however noted that there is limited data to support its use in thrombocytopenic patient samples. We discussed the next steps of the project to formalize the guidance document and a call to the community to contribute to our project.
Meeting Minutes

I. Speaker Presentation Notes

Platelet Physiology SSC: 2023 update - Sofia Ramström

The Platelet Physiology SSC chair Sofia Ramström started the session with an update on the progress with projects not presented elsewhere in the session. Three papers have been accepted for publication since the last ISTH meeting, two more are submitted and six are in preparation for submission during 2023. Several of these projects are performed in collaboration with other SSCs, namely Vascular Biology, Platelet Immunology, vWF and Genomics in Thrombosis and Haemostasis and Models of Thrombosis and Hemostasis SSC. She also introduced a new project recently receiving ISTH SSC Small Grant Funding, called “International multi-center validation of flow cytometry methods for the detection of Tissue Factor-positive platelets”. The Platelet Physiology SSC web page has been recently updated and the status for ongoing projects can now be seen at https://my.isth.org/communities/community-home?CommunityKey=b7e81e02-7e80-4268-9e49-e85e9720d8c0
**Update: Guidance Regarding Platelet Function Testing in Patients With Low Platelet Counts - Flow cytometry - Georges Jourdi**

Dr. Sharma and Dr. Jourdi presented an update of the project launched in collaboration between the Platelet Physiology and Platelet Immunology SSCs that aims to generate an international expert consensus on relevant methods for the evaluation of platelet functions in patients with thrombocytopenia. Dr. Jourdi presented the main results of the surveys and focus group discussions relative to flow cytometry assay which were summarized and recently submitted for publication. Briefly, the assay should be preferably performed on unseparated whole blood samples collected into buffered sodium citrate or thrombin inhibitor tubes. No minimal platelet count cut-off is required. Whole blood dilution ratio is usually 1:10 but in case of severe thrombocytopenia, a lower one might be necessary. Undiluted and adjusted-platelet-count control sample should preferably be included. Results should be interpreted with regard to local reference ranges. Standard agonist panels should include at least ADP, thrombin or TRAP, thromboxane A2 analogue and GPVI agonist. Standard platelet activation marker panels should include at least PAC-1 or fibrinogen binding and P-selectin, and if feasible, CD63, LAMP1 and annexin-V or lactadherin. Finally, the number of events to be collected can safely go down to 1000 events.

**Update: Guidance Regarding Platelet Function Testing in Patients With Low Platelet Counts: Aggregometry/Other methods - Ruchika Sharma**

Dr Sharma presented the platelet aggregometry part of the project described above. The process for this was reviewed. After project conception and approval, an expression of interest form was opened at the ISTH webpage. A second survey was circulated regarding pre-analytical, analytical, post-analytical and performance aspects of aggregometry for thrombocytopenic patients in 2022. 34 responses were received which helped identify areas of disagreement and paved the way for the focus group discussions. Two focus groups of experts in the field of whole blood aggregometry and light transmission aggregometry using platelet rich plasma were gathered, and the 2 focus group discussions were held in March 2023. The preliminary results of the survey and focus group discussions were summarized in the presentation.

We also discussed the next steps of the project to formalize the consensus document and a call to the community to contribute to our project.

**New project: Consensus protocol for quantification/detection of surface platelet glycans by using lectins - Dianne van der Wal**

Glycans (cell surface attached carbohydrates) are key in protein folding, cell adhesion, molecular trafficking, and cell signalling. In general, these glycan structures consist of different molecules i.e. N-acetylglycosamine, N-acetylgalactosamine, fucose, glucose and galactose and are typically capped by sialic acid. Removal of terminal N-glycans e.g. sialic acid (desialylation) is an “eat-me” signal for phagocytes and trigger the rapid removal of platelets. Desialylation is important in bacteremia, senescence, certain mutations, antibodies against glycoprotein Ibα and activation. To date, there is no standard protocol available for glycan-binding lectins. Recently, Lasne et al. obtained reference ranges for platelet surface galactose exposure using RCA-1 lectin from a large healthy population, but binding to other lectins is not standardised at all.
This collaborative project will evaluate methods for measurement of platelet glycans, by using glycan-binding lectins and Flow cytometry. A survey has just been completed and current methods used, positive and negative controls are being discussed.

**Final report/New project: Standardizing Platelet Transcriptomics and Proteomics: STRIDE and SWAP - Matthew Rondina and Joseph Aslan**

Matthew Rondina presented the final results of the STRIDE Study, an ISTH large grant funded, international, collaborative project comparing different platelet isolation techniques for next-generation RNA sequencing studies. He presented data suggesting that more stringent platelet isolation techniques reduces the number of leukocytes and relative expression of the leukocyte specific transcript PTPRC, without inducing platelet hyperactivation. More stringent platelet isolation techniques, however, were associated with significantly lower thrombin-induced integrin activation. Results were reproducible across sites in Italy, Hungary, and the US. These data will help guide laboratories on choosing the most appropriate isolation technique and are now being prepared for manuscript submission to JTH.

Joseph Aslan presented a new SSC project: Standardization of Washed Platelet Preparation Methods for Proteomic Analysis (The SWAP study). This project conceptually emerged following the London 2022 SSC session, and was discussed and refined by the SSC over the past year. Briefly, the SWAP study will first determine how washed platelet preparation methods vary between teams that specialize in human platelet proteomics, and develop a harmonized platelet washing protocol. Next, geographically distinct research groups with interest and ability will prepare platelets following the harmonized protocol and 2-3 agreed upon variations. The resulting samples will be sent to a single site (OHSU, Portland, OR, USA) for quantitative mass spectrometry analysis to determine whether and how platelet proteome content varies between sample prep conditions, location of origin and other variables of interest.

**Update: International multicenter assessment of methods to detect platelet dense granule deficiencies - Sofia Ramström and Dianne van der Wal**

Sofia Ramström and Dianne van der Wal presented an update regarding the project aiming to investigate the applicability of the more accessible flow cytometric methods to detect platelet dense granule deficiencies side-by-side with currently established techniques, for which a small grant from the ISTH has been received. The call for interested participants revealed that the original project plan needs to be slightly revised, as there were few labs able to run many methods in parallel, and in general, many labs had relatively few patients with well-defined defects available. Therefore, we have recently reached an agreement with the ISTH to re-write the budget plan in order to allow batch testing for some methods, and the project will now proceed with final decisions regarding the test protocols before patient enrollment begins.
Predictive and Diagnostic Variables in Thrombotic Disease Scientific Standardization Committee
27th June 2023 at 4pm
Montréal

Attendees:
Kerstin de Wit, Committee Chair
Anna Parks, Committee Co-chair
Rosa Talerico, Committee Co-chair
Erik Klok, Committee Co-chair
Scott Woller, Committee Co-chair
Helia Robert-Ebadi, Committee Co-chair
Camila Masias, Committee Co-chair

The meeting was well attended by committee members who gave important input and feedback for all projects.

Meeting Minutes

I. Call to Order
Dr de Wit opened the meeting, introducing the moderators Dr Talerico and Dr Parks

II. Agenda Review
Dr de Wit introduced the committee meeting presenters

III. Speaker Presentation Notes

Development of a Definition for Fatal Bleeding in Clinical Venous Thromboembolism Studies – update given by Tobias Tritschler
A short update of the project was presented at the SSC session. The objective of the project is to develop a consensus definition for fatal bleeding in clinical VTE studies. In a first step, a scoping review of prospective studies that evaluated anticoagulation for treatment of VTE was performed to summarize current definitions of fatal bleeding; the review has recently been published in the Journal of Thrombosis and Haemostasis (https://doi.org/10.1016/j.jtha.2023.02.013). Based on the definitions identified in the scoping review, the SSC working group developed a preliminary definition of fatal bleeding. In April 2023, the preliminary definition was incorporated in a Delphi survey of thrombosis experts. The preliminary definition and the results of the first round of the Delphi were presented at the SSC session. Furthermore, a live survey of the audience was conducted to guide the suggestion that will be incorporated in the second round of the Delphi. Next steps will be to complete the Delphi survey, discuss its results in a consensus meeting and, ultimately, suggest a new definition of fatal bleeding to the SSC.
Patterns of prescription of DOACs for the treatment of acute, proximal deep vein thrombosis (DVT) in elderly patients – update given by Camila Masias

There is an observed variability in the treatment of acute DVT in older patients. Factors unique to this population, such as higher prevalence of chronic kidney disease, frailty, polypharmacy, drug interactions, decrease adherence, both increase the risk of bleeding but and thrombosis. Providers tend to use dose reductions meant for stroke prevention due to this perceived risk of bleeding. To better characterize this problem, we performed a two-step survey; one conducted at ISTH 2022, among attendees to the SSC session, and an online survey directed towards providers from different geographic areas, levels of training and specialties.

Among the attendees to the SSC session in London 2022, apixaban was the preferred agent of choice for anticoagulation in elderly patients. There was a preference for dose reduction in treatment of DVT in elderly patients, with only 50%, 35% and 24.6% of responders opting for treatment dose according to the package insert in patients between the ages of 65-74, 75-84 and >85, respectively. For the online survey, so far we have 145 responses from 14 countries and 10 different specialties, as well as representation from pharmacists and advance practice providers (PAs and NPs). We are currently analyzing the results, and these will be published as an SSC communication.

The VTE-COS project – update given by Carol West

The VTE-COS project is to define a venous thromboembolism core outcome set for clinical research. The work is based on stakeholder consensus, including patients, caregivers, researchers, clinicians, policy makers and funders. There is currently no formal consensus on which outcomes should be measured in VTE trials, and patient-reported outcomes are especially lacking. There is a need for standardization across studies and between countries. Patients account for 33 of 41 qualitative interviews, across 8 countries, and form the heart of the VTE-COS project. A Delphi survey will be launched in several months’ time, and participation is encouraged from all stakeholders, who will benefit from the standardization resulting from a VTE core outcome set. The opportunity represented by VTE-COS for patient to be engaged at all stages of the project is meaningful and appreciated.

Standardized reporting and analysis for diagnostic studies in venous thromboembolism – presented by Ludovica Cimini

The quality assessment of studies included in meta-analysis is a crucial step as can lead a controversial result. This study was aimed at assessing the reliability and repeatability of three existing tools for quality assessment of non-randomized studies (QUADAS2, NOS and ROBINS-I) and comparing the assessment by tools with implicit assessment by an expert reviewer (considered as the gold standard). Studies selected for a previous meta-analysis on echocardiography in acute pulmonary embolism were independently rated by four reviewers with the QUADAS2 tool, the ROBINS-I and the NOS scores. Each of these studies was reviewed also by an expert reviewer and classified according to his experience as low, intermediate, or high quality. An inter-rater reliability analysis, as well as a comparison with the expert reviewer ratings, were performed. The summary score of NOS had a slight agreement (Gwet’s AC1 coefficient 0.18, 95% CI 0.12-0.25), Robins-I overall risk of bias judgement had fair agreement (Gwet’s AC1 coefficient 0.38, 95% CI 0.28-0.47). The agreement at domain level and item level varies widely across the three tools. The QUADAS2, specific for diagnostic studies, showed a poor agreement. The comparison between the tools assessments and the expert reviewer assessment showed a significant difference using the NOS. Currently, an item response analysis is ongoing. In existing tools, some domains, and items, as well as at a tool level, showed a modest agreement reliability. Each of the assessed tools includes critical items based on the type of assessed study or the skills of the reviewer. These results highlight the need for improvement of quality assessment tools and can inform the process of improvement.
Re-evaluating the ISTH definitions of major bleeding and clinically relevant non-major bleeding - update given by N. Guman

There are some challenges with the implementation of current ISTH major bleeding and clinically relevant non-major bleeding definitions. This project will aim to re-evaluate and summarize the components of bleeding definitions classifications; and to develop standardized criteria to assess the severity of anticoagulant-related major bleeding events. This will be completed with a systematic review of the literature, summarizing definitions and incidence of bleeding definitions components, draft guidance, and online questionnaire of experts.

Standardized reporting and analysis for diagnostic studies in venous thromboembolism– update given by Tobias Tritschler

A short update of the project was presented at the SSC session. The objectives of the project are to evaluate and summarize reporting and methods for analysis in recent diagnostic management studies of patients with suspected VTE, and to develop recommendations for standardized reporting and analysis for diagnostic management studies in VTE. To achieve these objectives, the following steps are planned: 1) scoping review; 2) drafting of a preliminary guidance document on essential items for reporting and analysis of diagnostic management studies in VTE; 3) Delphi survey on proposed items; and 4) propose a final guidance statement to the SSC. At the SSC session, the rationale for the project and the preliminary results of the scoping review were presented. Next steps will include to complete the scoping review, draft a preliminary guidance document and conduct the Delphi survey.

VTE outcome set - update given by Samarth Mishra

Preliminary research shows that patients diagnosed with PE suffer from sustained psychological distress, loss of self, and poor experiences at medical facilities. There is a clear need for improvement of communication for VTE diagnoses. The development of a VTE Communication Toolkit will provide providers a guide for what to inform patients, how the information should be communicated, and when it is most suitable to share information. Furthermore, the development of a toolkit also aims to make VTE diagnosis information more accessible to patients through digital resources including social media, articles, support groups, and potentially even apps.

Risk stratification for acute pulmonary embolism – update given by Erik Klok

The SSC intends to initiate a new project that is aimed at providing guidance in evidence-based medicine triaging of patients with acute pulmonary embolism (PE). Its rationale is that numerous (imaging) biomarkers, vital parameters and risk scores are available and validated to predict risk of death or early adverse outcome in patients with acute PE. All of these provide an absolute risk of death or adverse events, a number that is difficult to interpreted. The mean reason for this is that management studies that have (consistently) shown that applying a certain risk assessment method leads to good or better clinical outcomes are mostly unavailable. For that reason, guidelines are mostly based on epidemiological data and often differ in their recommendations. We will perform reviews of the literature of 5 important management decisions to establish if and which risk assessment tool can be used to guide these decisions according to adequate evidence. These 5 decisions are: 1) to hospitalize the patient, 2) to start hemodynamic monitoring of the patient, 3) to admit the patient to an intensive/critical/coronary care department, 4) to start reperfusion therapy and 5) to discharge the patient. We hope to have published the results of this project within 2 years from start of the project.
IV. **Conclusion**
The subcommittee is working on a diverse range of standardization projects. Each project has set out the goals for the coming year. Updates will be presented in 2024.
Attendees: Kimberly Martinod (chair), Constantino Martinez (co-chair), Johannes Thaler (co-chair), Yohei Hisada (co-chair), Ruben Bierings (co-chair), Chloé James (co-chair), David Smadja (former co-chair), Bas Laan (invited speaker)

Chair and Co-chairs: Kimberly Martinod (chair), Constantino Martinez (co-chair), Johannes Thaler (co-chair), Yohei Hisada (co-chair), Ruben Bierings (co-chair), Chloé James (co-chair), Coralie Guerin (co-chair), Claudine Graf (co-chair)

- 16:30 – 16:35 ET

SSC 17.1 - Session Introduction and Overview

**Presenter:** Kimberly Martinod, PhD – Center of Molecular and Vascular Biology, Department of Cardiovascular Sciences, KU Leuven, Leuven, Belgium

**Summary:** Dr. Martinod opened the session by introducing the new co-chairs of this SSC as of 2023: Yohei Hisada (UNC, USA), Chloé James (Bordeaux, France), Coralie Guerin (Institut Curie, France) and Constantino Martinez (Murcia, Spain). Previous chair Johannes Thaler (Vienna, Austria) and co-chair Claudine Graf (Mainz, Germany) rotate off as members of the SSC this year. The priorities of the Vascular Biology subcommittee were highlighted as (1) Extracellular vesicles / Tissue factor-positive EVs, (2) circulating endothelial cells / endothelial colony forming cells, and (3) neutrophil extracellular traps and immunothrombosis. Two communications recently published online in JTH were highlighted: Joseffson et al., “Consensus report on markers to distinguish procoagulant platelets from apoptotic platelets: communication from the Scientific and Standardization Committee of the ISTH” jointly with the Platelet Physiology SSC published in May 2023, and Blandinieres et al., Results of an international survey about methods used to isolate human endothelial colony-forming cells (ECFCs): Guidance from the Scientific and Standardization Committee on Vascular Biology of the International Society of Thrombosis and Hemostasis published in June 2023. Two further SSC projects (both funded with small project grants) have been completed in 2022/2023: (1) Comparison of assays measuring extracellular vesicle-tissue factor in plasma samples led by Romaric Lacroix and (2) A recommendation for measurement of neutrophil extracellular traps in human plasma samples led by Kim Martinod. The session was closed with an overview of the subsections of the session (NETs, TF-EVs, then CEC/ECFCs), a call for next co-chair applications and new projects, and a notice to look for a name change for the subcommittee in 2024, to be announced if approved by the Executive Committee.
SSC 17.2 - NETs session

Moderator: Kimberly Martinod, PhD – Center of Molecular and Vascular Biology, Department of Cardiovascular Sciences, KU Leuven, Leuven, Belgium

- 16:35 – 16:40 ET

SSC 17.3 - Status of ISTH-NETs standardization 2023

Speaker: Kimberly Martinod, PhD – Center of Molecular and Vascular Biology, Department of Cardiovascular Sciences, KU Leuven, Leuven, Belgium

Summary: Dr. Martinod gave a summary of the current status of the NETs standardization project from this SSC. In 2020, a survey was sent out ISTH-wide to query researchers about the type of samples they analyze for NETs, pre-processing steps, and analytical variables assessed for qualitative and quantitative purposes. The survey also served to recruit participants for Phase 1 of the lab study, a comparative analysis of ex vivo generated NET fragments using their existing methodology. Phase 2 proceeded with recommendations for assays from consensus from all Phase 1 participants. With an SSC grant funded in 2023, a Phase 2 expansion phase begins which was introduced to the attendees, including more centers (recruitment open), analysis of pre-analytical variables, and validation in patient plasma cohort samples. The study proceeds with the recommended assays from 2022’s SSC session as well as with the Nu.Q assay introduced this year as a CE-marked assay for NET-derived nucleosomes. Material will be donated by VolitionTx for this part of the study. Expected start is fall 2023 and the talk closed with a call for participants.

- 16:40 – 16:55 ET

SSC 17.4 - miRNAs, NETs, and Cardiovascular Disease

Speaker: Constantino Martinez, PhD – Servicio de Hematología y Oncología Médica, Hospital Universitario Morales Meseguer, Centro Regional de Hemodonación, IMIB-Pascual Parrilla, Murcia, Spain

Summary: Dr. Constantino Martínez made an overview on the role of microRNAs in thromboinflammation. Their role in the control of platelet and neutrophil function still needs active investigation, especially in NETosis. miRNAs are also interesting diagnostic and prognostic markers for CVDs although an important effort must be done concerning methodological standardization. A survey to know the collection, processing, and quantification of blood miRNAs in the thrombosis and haemostasis field is proposed.

- 16:55 – 17:00 ET

SSC 17.5 - Question/Answer Session
**Moderator**: Kimberly Martinod, PhD – Center of Molecular and Vascular Biology, Department of Cardiovascular Sciences, KU Leuven, Leuven, Belgium

- 17:00 – 17:45 ET

**SSC 17.6 - Extracellular Vesicles session**

**Moderator**: Johannes Thaler, MD, PhD (he/him/his) – Clinical Division of Hematology and Hemostaseology, Department of Medicine I, Medical University of Vienna, Austria

- 17:00 – 17:15 ET

**SSC 17.7 - Summary of the problematic TF measurements using cutting-edge technologies**

**Speaker**: Yohei Hisada, PhD – University of North Carolina at Chapel Hill

**Summary**: Dr. Yohei Hisada summarized the problematic tissue factor measurements using cutting-edge technologies. Cutting-edge technologies need to be carefully evaluated before concluding that they can be used to measure levels of tissue factor in plasma. It is important to use appropriate positive and negative controls and use well characterized anti-tissue factor antibodies when measuring tissue factor.

- 17:15 – 17:30 ET

**SSC 17.8 – Extracellular vesicles in human milk and other body fluids**

**Speaker**: Johannes Thaler, MD, PhD (he/him/his) – Clinical Division of Hematology and Hemostaseology, Department of Medicine I, Medical University of Vienna, Austria

**Summary**: Dr. Johannes Thaler reported that in the 1930s superficial bleedings in patients with hemophilia were effectively treated with tamonades soaked in human milk. This was the first effective hemophilia treatment. Only recently the coagulant properties of human milk were rediscovered, when it was shown that human milk contains highly coagulant tissue factor and factor VIIa complex exposing extracellular vesicles. Such coagulant extracellular vesicles are also present in amniotic fluid, tears, saliva, and urine. These physiologic body fluids also lyse formed fibrin clots and the fibrinolytic activity is inhibited by aprotinin, indicating the presence of plasmin. Finally, Dr. Thaler proposed that physiologic body fluids provide additional hemostatic protection and suggested an "extended hemostatic envelope model".

- 17:30 – 17:45 ET

**SSC 17.9 - Question/Answer Session**
17:45 – 18:30 ET

**SSC 17.10 - CEC/ECFC session**

**Moderator:** Ruben Bierings, PhD – Department of Hematology, Erasmus MC, University Medical Center Rotterdam, the Netherlands

- 17:45 – 17:55 ET

**SSC 17.11 - Extravascular involvement of endothelial cells and their progenitors in cardiovascular disease**

**Speaker:** David Smadja, PhD (he/him/his) – Université Paris Cité

**Summary:** Dr. Smadja gave a short update about the recently published SSC communication titled, published this week at JTH. He introduced background information on extravascular involvement of endothelial cells and their progenitors in cardiovascular disease, and presented unpublished data supporting targeting ECFCs with an undisclosed compound in preclinical cardiovascular disease models.

- 17:55 – 18:10 ET

**SSC 17.12 - Transcriptome and functional analyses of ECFC clones**

Room: 710B

**Speaker:** Bas Laan, PhD – Leids Universitair Medisch Centrum

**Summary:** Bas Laan presented his study where they investigated the phenotypic heterogeneity of endothelial colony forming cells (ECFCs) derived from healthy donors, aiming to understand their differences in gene expression and morphology. 33 ECFC clones from 16 healthy controls were analyzed, with a focus on gene expression related to Weibel-Palade body (WPB) proteins, Von Willebrand Factor (VWF) transcription factors, and endothelial cell markers. The study also conducted phenotypic profiling using confocal microscopy and automated WPB segmentation. Results revealed two major clusters of ECFCs with distinct RNA expression patterns, driven by differences in various gene expressions. Additionally, cluster one ECFCs had more WPBs compared to cluster two ECFCs, which had shorter and rounder WPBs. These findings emphasize the importance of considering these differences when using ECFCs as endothelial models for vascular disease and suggest the need for careful selection of ECFC clones with similar characteristics in research involving patient-derived ECFCs.

- 18:10 – 18:25 ET

**SSC 17.13 - The study of Circulating Endothelial Cells (CEC) to analyze patient Ecs**

Room: 710B

**Speaker:** Chloe James, MD PhD (she/her/hers) – University of Bordeaux
Endothelial cells are involved in the pathogenesis of thrombosis but are currently poorly explored in patients with unexplained thrombosis. Chloe James discussed the rationale to set up protocols to efficiently sort circulating endothelial cells in order to be able to genotype them. Some assays have been developed but need to be carefully evaluated to make sure endothelial cells have been indeed sorted. New protocols should be implemented and validated by different groups.

- 18:25 – 18:30 ET

SSC 17.14 - Question/Answer Session and Session Conclusion
Room:710B

Moderator: Ruben Bierings, PhD – Department of Hematology, Erasmus MC, University Medical Center Rotterdam, the Netherlands

Dr. Bierings led the Q&A and closed the session.
Women’s Health Issues in Thrombosis and Hemostasis  
June 24, 2023

Attendees:
Robert F. Sidonio, Jr. MD, MSc, Chair (moderator)
Kinga Malinowski, MD, MSc, Co-chair
Katie Yeung (medical student), guest speaker
Rezan Kadir, MD, Co-chair
Offer Erez, MD, Co-chair (moderator)
Nathan Connell, MD, MPH, guest speaker
Angela Weyand, MD, Co-chair (moderator)
Rohan D-Souza MD, PhD, guest speaker

Meeting Minutes

I. Speaker Presentation Notes

A. Speaker 1 (Kinga Malinowski, MD, MSc) presentation: Registry on knowledge, practice, management and outcomes on pregnancy & COVID-19. Dr. Malinowski outlined her ISTH SSC project on what we learned regarding COVID and pregnancy and the utilization of anticoagulants. She presented data on the cases in preparation for her manuscript submission.

B. Speaker 2 presentation (Katie Yeung) presentation: Etiology and Diagnosis of HMB in adolescent and pre-menopausal patients. Mrs. Yeung reviewed the progress made on her ISTH SSC project focused on her systematic review of the etiology and diagnosis of HMB related and unrelated to a congenital bleeding disorder. The overall prevalence on a congenital bleeding disorder in cases of HMB was 30.1%, higher in children compared to adults. While the prevalence of VWD was 10%, again higher in children however it was 8.4% for QPD, higher rates noted in adults. The review identified a lack of clear HMB definition, and a paucity of studies focused on evaluation, a clear referral bias and lack of larger population studies outside the university setting. The next steps are to submit a manuscript for the cmte to review.
C. Speaker 3 presentation (Rezan Kadir, MD): Severe protein C deficiency: A retrospective study of a rare disorder. Dr. Kadir presented a number of cases collected as part of her ISTH SSC project with a focus on providing clarity on diagnosis and management of this rare but life-threatening condition. The prevalence of severe congenital protein C deficiency (SCPCD) is lower than expected, possibly because of fetal loss or death in early infancy without diagnosis. This study investigates retrospectively the obstetric history of mothers of patients with SCPCD. Clinicians known to have patients with SCPCD were asked to submit data to the ISTH REDcap site. So far, data has been submitted from 10 families. Four mothers had a history of early miscarriage, one having 6 miscarriages. There were no late miscarriages. Two mothers had a history of intrauterine death (cerebral haemorrhage in 1 case). Three couples had experienced neonatal deaths not thought at the time to be due to SCPCD. One case had purpura fulminans. One couple had a history of 3 previous neonatal deaths. Early data suggests an association with fetal loss and early neonatal death in previous pregnancies.

D. Speaker 4 presentation (Rozan D’Souza, MD PhD): Understanding shared decision-making process on anticoagulant choice for pregnant patients with mechanical heart valves. Dr. D’Souza presented on behalf of Dr. Shehata as part of a recently funded ISTH SSC project. They presented their interim data and rationale for this ongoing study. The aim is to understand this process and the clinical factors that influence this decision making and to explore the values and preferences of HCPs that shape the decisions for the choice of optimal anticoagulant in this setting. The study will involve hematologists, internists, OB-GYN, and cardiologists and currently the study group is in the interview portion of the study. Purposive sampling will be conducted to try and ensure inclusion of HSUs that represent diversity in several variables. As with qualitative research studies, interview recordings will be transcribed for conventional content analysis and data analysis will be conducted iteratively alongside conduct of interviews to establish data saturation and inform HCP interviews. They anticipate completion in late 2024.

E. Speaker 5 (Nathan Connell, MD, MPH) presentation: How should we approach clinical research in hematology in transgender persons: challenges and solutions. Dr. Connell discussed the intersectionality of the thrombotic and bleeding disorder community with those who identify as LGBTQIA+. Specific issues in the care of transgender persons were discussed including the evolution of gender inclusive terminology, the use of hormone therapy and surgery to achieve
embodiment goals, and the published reviews and trials on prevention of thrombosis and hemorrhage in this population. The session included discussion on the social implications of thrombosis hemostasis research in transgender persons and how approaching research in this area with a lens of harm reduction would improve care moving forward. We concluded that ISTH should work to further understand the specific needs of this population and consider creating a working group to prioritize future work in this field focused on appropriate data terms.

II. **Conclusion/Any additional notes**

A. Ongoing ISTH SSC project updates.
   i. Shehata, Nadine. “Understanding shared decision making process regarding the choice of anticoagulant for pregnant patients.”
      1. Project approved for small grant. Underway and presented at ISTH 2023 meeting.
   ii. Belizna, Christina. Joint project with Lupus anticoagulant group. “CORA international registry”
      1. Delays related to change in institution of the PI. Enrolling as of July 2023.
   iv. Malinowski, Kinga. “Physicians knowledge and practices of management of COVID coagulopathies in pregnancy” and International registry on pregnancy COVID coagulopathy and thrombosis”
      1. Enrollment complete. Submitted manuscript to JTH. Final manuscript in preparation with major revisions. Will have 2 manuscripts from these related projects.
      1. Paper submitted and accepted and guidance document being created.
   vi. Malinowski, Ann. “Immune thrombocytopenia and obstetric neuraxial anesthesia with low platelet counts”
      1. Difficulty enrolling but ongoing project.
   vii. Minford, Adrian. “Retrospective Obstetric study on severe protein C deficiency.”
   viii. Blondon, Marc. “Registry for invasive treatments for massive PE during pregnancy or post partum period.”
1. Planned systematic review and evaluate whether feasible to continue due to slow enrollment.

ix. Need to add previous approved projects:
   1. Weyand, Angela. “Risk of thrombosis in users or concurrent hormonal contraceptives and TXA.” Study underway.